Protocol Title:

Combined Intrathecal and Intravenous VTS-270 Therapy for Liver and Neurological Disease Associated with Niemann-Pick Disease, type C1

Abbreviated Title: IV VTS-270 therapy for NPC1

Protocol Number: 19-CH-0028

Date of This Submission/Version: July 2nd, 2021/Version 6

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Human Research Protections Program Investigator and Staff Training:

Training of individuals working on this protocol will.

Total requested accrual

18 Patients
0 Healthy Volunteers

Project Uses Ionizing Radiation: □ No X Yes
. Medically-indicated only
. Research-related only
X Both

IND/IDE □ No X Yes
Drug/Device/# IND 142671
Sponsor: _____ NICHD_____

Durable Power of Attorney □ No X Yes

Multi-institutional Project X No □ Yes
Institution#1_____N/A_____ FWA #_____
Date of IRB approval _____

Institution#2_____N/A_____ FWA #_____
Date of IRB approval _____

Data and Safety Monitoring Board X No □ Yes

Technology Transfer Agreement □ No X Yes
Agreement type and number CRADA 03272_____

Samples are being stored □ No X Yes

Flesch-Kincaid reading level: Consent – 10.4; Assent – 6.4 _____

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Précis:

Niemann-Pick disease type C (NPC) is a lethal, autosomal recessive, lysosomal storage disorder characterized by neurodegeneration in early childhood and death in adolescence. NPC results from mutation of either the *NPC1* (~95% of cases) or *NPC2* genes. Biochemically, NPC is characterized by the endolysosomal storage of unesterified cholesterol and lipids in both the central nervous system and peripheral tissues such as the liver. Individuals with NPC demonstrate progressive cerebellar ataxia and dementia. Acute cholestatic liver disease is frequently observed in the neonatal/infantile period but subsequently resolves. However, chronic, sub-clinical liver disease persists. Intrathecal 2-hydroxypropyl-β-cyclodextrin (HPβCD, VTS-270) has proven effective in reducing signs and prolonging life in NPC1 animal models, and Phase 1/2a data support efficacy in NPC1 patients. Parenteral administration of VTS-270 has also been shown to be effective in treating liver disease in the NPC1 cat.

In this Phase 1/2a, open-label, randomized, parallel dose, single-center study, we will examine whether VTS-270 can be used to treat chronic subacute liver disease in NPC1 patients. Our primary objective is to determine the safety and tolerability of intravenous VTS-270 in NPC1 disease. Secondary objectives will be to evaluate the efficacy of VTS-270 to reduce plasma cholestane-3β,5α,6β-triol, an NPC1-specific pharmacodynamic biomarker, and to normalize the degree of liver injury. Exploratory testing will include lipid and protein biomarkers. This study will evaluate three dose levels (500, 1000 and 1500 mg/kg) administered monthly for twelve months. Safety will be assessed by adverse event recording, clinical laboratory testing and physical examination. Clinical efficacy will be evaluated by assessment of liver chemistries, determination of liver size and liver stiffness. Biochemical efficacy will be assessed by measurement of plasma cholestane-3β,5α,6β-triol and other biomarkers.

List of Abbreviations

Abbreviations	Description of Abbreviations
24(S)-HC	24-(S) hydroxycholesterol
ABR	Auditory brainstem response
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
AUA	American Urological Association
AUC	Area under the curve
AUC_{0-t}	Area under the plasma or CSF concentration-time curve from zero (0) hours to time (t)
BAER	Brain stem auditory evoked response
Caregiver-CGIC	Caregiver-Clinical Global Impression of Change
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
Clinician-CGIC	Clinician-Clinical Global Impression of Change
Cmax	Maximum plasma concentration
CNS	Central nervous system
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DPOAE	Distortion Product Otoacoustic Emission(s)
DSC	Dose Selection Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate

Abbreviations	Description of Abbreviations
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GRAS	Generally regarded as safe
HPβCD	2-hydroxypropyl-β-cyclodextrin
IC	Intracisternal
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICV	Intracerebroventricularly
IEC	Independent Ethics Committee
iIND	Investigator Sponsored Investigational New Drug Application
IND	Investigational New Drug Application
IRB	Institutional Review Board
IT	Intrathecal
IUD	Intrauterine device
IV	Intravenous
LE/LY	Late endosomal/lysosomal
LP	Lumbar puncture
LSOs	Lysosomal storage organelles
mITT	Modified intent-to-treat
NCI	National Cancer Institute
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NOAEL	No observable adverse effect level
NPC	Niemann-Pick disease, type C
NPC/Npc1 and *NPC2*	Genes that, when mutated, cause NPC phenotypes
NPC1	Niemann-Pick disease, type C1
PT	Prothrombin time
PTA	Pure Tone Audiometry

Abbreviations	Description of Abbreviations
QoL	Quality of life
SAE	Serious adverse event
SC	Subcutaneous
SCr	Serum creatinine
SD	Standard deviation
SE	Standard error
SOP	Standard operating procedure
SPL	Sound pressure level
SUSAR	Serious and unexpected suspected adverse reaction
TUG	Timed up and go
ULN	Upper Limit of Normal
US	United States
$V_{d,ss}$	Volume of distribution at steady-state
VSNGP	Vertical supranuclear gaze palsy

1. Introduction and Background

1.1 Niemann-Pick disease, type C1

Niemann-Pick disease, type C (NPC) is a recessive lysosomal storage disorder characterized by impaired intracellular trafficking and subsequent endolysosomal accumulation of unesterified cholesterol and other lipids in the central nervous system and visceral organs [2]. NPC results from mutation of either the *NPC1* or *NPC2* genes, with the vast majority (~95%) of cases due to impaired NPC1 function. Incidence of classical NPC has been estimated to be on the order of 1/89,000-104,000 with potential of a late-onset variant of NPC1 with incidence on the order of 1/36,000 [2, 3]. The NPC1 phenotype is heterogeneous with respect to both age of onset and symptom complex. Visceral disease including hepatosplenomegaly and cholestatic jaundice of variable severity can be present in early childhood and is followed by progressive neurological disability [4, 5]. Common neurological signs and symptoms include vertical supranuclear gaze palsy, cerebellar ataxia, gelastic cataplexy, seizures and cognitive impairment. An adult-onset variant with prominent psychiatric symptoms has recently been characterized [6]. Diagnosis of NPC1 is frequently delayed, but the recent

development of a serum-based diagnostic test will facilitate earlier diagnosis [7-9]. There are no FDA approved therapies for NPC1, although miglustat (Zavesca®) has been approved for use in the European Union and multiple other countries [10-13] based on a controlled trial and long-term extension studies.

1.2 Liver Disease in Nieman-Pick disease, type C1

In infantile and juvenile forms of the disease, patients frequently present with cholestasis or hepatosplenomegaly. NPC has been reported to be the second most common genetic metabolic disorder in neonatal liver disease [14], and was diagnosed in up to 8% of neonates presenting with intrahepatic cholestasis in one case series [15]. In the majority of cases the liver disease becomes subacute, although in other cases the liver disease can progress to liver failure. In the majority of cases, liver inflammation and dysfunction persist, as evidenced by chronic elevations in serum transaminases and abnormal prothrombin (PT) and partial thromboplastin (PTT) times. Approximately two-thirds of NPC1 subjects enrolled in the NIH Natural History study (06-CH-0186) have had elevated serum transaminases. Liver disease in NPC can result in a lethal degree of hepatic fibrosis and the chronic disease predisposes to hepatocellular carcinoma [16-19]. Although Phase 1/2a trial data indicates that IT therapy has an impact in slowing neurological disease progression [1], direct CNS delivery appears unlikely to have an effect on peripheral disease, based on liver chemistries. In the NPC1 cat model subcutaneous administration of 2-hydroxypropyl-β-cyclodextrin (HPβCD) 1000 mg/kg biweekly (11 treatments over 21 weeks) reduced serum ALT from ~6-fold elevated to 2-fold elevated [20]. This was accompanied by correction of the severe vacuolization of hepatocyte and Kupffer cell cytoplasm observed in untreated cats. In human NPC1 patients dosed under an individual IND, IV administration of HPβCD (2500 mg/kg biweekly) reduced by 2-fold plasma cholestane-3β,5α,6β-triol [21], an NPC disease-specific biomarker that monitors oxidizable free cholesterol in liver tissue [8]. Taken together, the preclinical and human data suggest that IV HPβCD may be effective in reducing liver inflammation and injury and may prevent the long-term sequelae, such as cirrhosis and risk of hepatocellular carcinoma.

1.3 Investigational Product Description

HPβCD, a generally regarded as safe (GRAS) substance, is a membrane-impermeant cyclic oligosaccharide with a distinctive truncated cone configuration containing 7 cyclo-α-(1,4)-anhydroglucose units with hydroxypropyl groups randomly substituted onto the C2, C3 and C5 positions of the substituent glucoses (Fig. 1). All HPβCDs are amorphous mixtures of different isomers, characterized by the degree of substitution, which represents the average of substitution of the hydroxyl with propyl groups per HPβCD molecule.

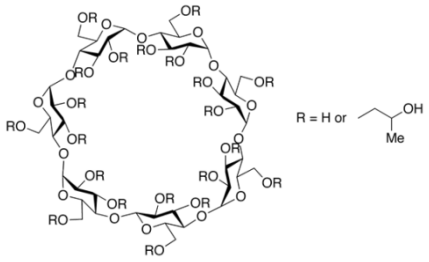

Figure 1. VTS-270, HP-β-CD

The active drug substance in VTS-270 is KLEPTOSE® HPB parenteral grade, which has an average degree of substitution of 4.34 or on a molar basis of 0.63 ± 0.01.

Cyclodextrins, as well as HPβCDs in general, are used extensively to solubilize pharmaceuticals and various regulatory authorities have approved them as excipients. HPβCD is a cyclic polysaccharide that can be used to solubilize hydrophobic compounds such as cholesterol. The potential therapeutic efficacy of HP-β-CD was first investigated by Camargo et al [22] utilizing a NPC1 mouse model [23, 24], but only slight neurological efficacy was observed. Subsequent studies by Liu et al [25, 26] and Davidson et al [27] demonstrated delayed progression of neurological signs and death in *Npc1* mutant mice. Therapeutic efficacy has also been demonstrated in the feline NPC1 model [20].

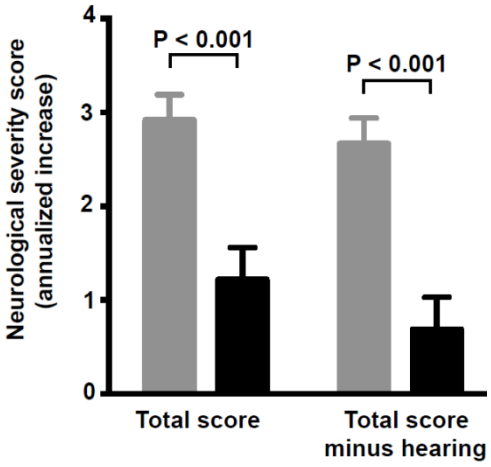

Figure 2. NPC1 neurological disease progression is significantly decreased in 14 NPC1 subjects treated with intrathecal VTS-270 (black) compared to an age similar cohort of 21 Natural History participants

HPβCD enters cells by the endocytic pathway and is delivered to the endolysosomal storage organelles where unesterified cholesterol accumulates in NPC deficiency. HPβCD replaces the function of NPC1 protein and promotes transport of the accumulated unesterified cholesterol to the endoplasmic reticulum for esterification by acetyl CoA cholesterol:acyl transferase, and subsequent efflux [28, 29]. While the precise mechanism of HPβCD action to bypass or replace NPC1 function is not yet defined, HPβCD normalizes intracellular cholesterol trafficking by binding the hydrophobic moieties of cholesterol and other lipids.

HPβCD does not efficiently cross the blood-brain-barrier [30], thus necessitating the use of extremely high peripheral doses or direct intrathecal infusion to reach the CNS. A Phase 1/2a trial of intrathecal VTS-270 has been conducted at the NIH Clinical Center, and the 18-month data demonstrates a significant stabilization of neurological disease progression ([1]; Figure 2). Based on these data, a multicenter, multinational Phase 2b/3 trial of intrathecal VTS-270 was initiated in the fall of 2015. With the development of a potentially effective therapy for the neurological aspects of NPC1, consideration needs to be given to the treatment of visceral issues.

1.3.1 Non-clinical Toxicology Studies

The pharmacological properties of HPβCD have been extensively studied in *Npc1*$^{-/-}$ mice and NPC1 cats. The pharmacokinetic properties have been studied

in rats, dogs, and the *Npc1*$^{-/-}$ mice and NPC1 cats. The safety of HPβCD was evaluated in a comprehensive toxicology program conducted by Janssen Research Foundation (Janssen) to support its use as a pharmaceutical excipient. Preclinical toxicology studies included single and repeat-dose toxicity studies, in vitro and in vivo genotoxicity assays, carcinogenicity studies, reproductive and developmental toxicity (Segment I, II and III) studies and special toxicity (local tolerance and mechanistic toxicity) studies. HPβCD has been approved for use as an excipient in oral and intravenous (IV) pharmaceuticals for over a decade. Mallinckrodt, the supplier of the drug, has obtained the rights to reference the Roquette Freres Type IV Drug Master File No. 9420 for HPβCD, the drug substance. Mallinckrodt will provide a letter of reference to the VTS-270 IND to support this investigator sponsored trial.

1.3.2 Acute Toxicity Studies

After a single IV dose of HPβCD, mortality occurred in mice at a dose ≥ 10,000 mg/kg body weight. The most common clinical abnormality at all dose levels (5,000-20,000 mg/kg body weight) in mice was viscous urine. At lethal doses, typical signs of toxicity included soft feces, sedation, piloerection, clonic convulsions, dyspnea, hypothermia, loss of righting reflex, palpebral ptosis, and tremors. IV doses of 2,000 and 4,000 mg/kg body weight were not lethal in rats but did result in hyperemia. Rats in the 4,000 mg/kg body weight group also were observed with viscous urine, hypotonia, ataxia, and swelling of the ears, nose, and paws. Dogs survived single IV doses of 5,000 mg/kg body weight HPβCD. No clinical abnormalities were noted in the females, but coughing, diarrhea/soft feces, and emesis were observed in the males.

1.3.3 Repeat Dose Toxicity Studies

Repeat dose studies utilizing IV administration were performed in rats and dogs. Urinary tract changes were present after IV administration and included swollen and granular tubular cells in the kidney, swollen epithelial cells in the urinary bladder and renal pelvis, and vacuolated cortical tubules in the kidney. The no-observed-adverse-effect-levels (NOAELs) in the 3-month IV studies were 50 mg/kg body weight in the rat and 100 mg/kg body weight in the dog. In rats, higher doses (100 and 400 mg/kg body weight) led to reduced body weight gain. Hematological changes and altered serum chemistry were seen at the highest dose (400 mg/kg body weight). Urinary parameters were slightly modified and included increases in white blood cells, cylindrical epithelial cells, occult blood, and granular casts and decreases in specific gravity and creatinine associated with larger urine volume. Adrenal gland, spleen, and kidney weights were increased. Kidneys were pale at necropsy. Histological changes in the liver and lung included increased presence of Kupffer cells in the liver and foamy cells and white stipples in the lung. Following the 1, 2, or 3 months of recovery, most of these changes reverted to normal. After 3 months of recovery, the only remaining abnormalities were slightly elevated liver transaminases (400 mg/kg body

weight), pale kidney (100 and 400 mg/kg body weight), swollen epithelial cells in the urinary bladder and pelvic epithelium (all doses levels). The corticotubular changes resolved completely (25 mg/kg body weight), almost completely (50 mg/kg body weight) or were partially reversible (100 and 400 mg/kg body weight). In dogs, IV administration of 400 mg/kg body weight, HPβCD led to transient soft feces and slightly elevated alanine aminotransferase (ALT) and bilirubin or haptoglobin. Macroscopic and microscopic (foamy cells) lung changes were seen as well. All of these changes resolved after 1 month of recovery. At the end of the 3-month recovery, swollen epithelial cells were seen in the urinary bladder and renal pelvis but vacuolated cortical tubules (with swollen lysosomes) were not found any longer. Repeat-dose studies extracted from the literature also support these findings [31].

1.3.4 Reproductive and Developmental Toxicity Studies

Reproductive function (fertility) was not adversely affected by IV administration of HPβCD in rats. Maternal and paternal toxicity was limited to a slight reduction in body weight. No primary embryotoxicity was noted following IV administration in rats or rabbits. Associated with maternal toxicity, decreased survival and reduced birth weight and body weight evolution of the rat pups were noted at 400 mg/kg body weight. In a 2nd un-dosed generation, all variables were normal. No developmental toxicity was noted in any study.

1.3.5 Genotoxicity

The genotoxic potential of HPβCD was investigated in Ames tests (*S. typhimurium* and *E. coli*), a mammalian cell assay, chromosome aberration test, micronucleus tests, and deoxyribonucleic acid (DNA) repair tests. No mutagenic potential was evident in any of these studies.

1.4 Previous and Ongoing Human Experience with Intravenous HPβCD

The investigators are aware of eight NPC1 patients in the US being dosed with IV HPβCD supplied by Johnson & Johnson/Janssen with the intent to treat CNS disease under expanded use INDs. Doses up to 2500 mg/kg were infused over eight hours (312.5 mg/kg/hr) twice per week. Matsuao et al [32] reported on two NPC1 subjects who were given up to 2000 or 2500 mg/kg two or three times per week. Transient diffuse pulmonary cloudiness and fever were reported, perhaps due to an infusion reaction, in one subject dosed with 2500 mg/kg. Decreased liver size and AST level were observed in this same subject after 3-4 months of therapy. The FDA has approved at least three emergency INDs for IV VTS-270 treatment of neonatal liver disease in NPC1. As part of our effort to evaluate the role of IV HPβCD in the treatment of NPC1 liver disease, a complementary study involving infants is being conducted at St. Louis Children's Hospital. This study (NCT03471143) has been approved by the Washington University IRB and is conducted under IND#136489.

The investigators are aware of two other unaffiliated studies (NCT02912793, NCT02939547) which are evaluating a different preparation of IV HPβCD.

1.4 Study Rationale

As described earlier (section 1.2), chronic, subacute liver inflammation persists beyond the infantile period. Approximately two-thirds of NPC1 participants enrolled in the NIH Natural History study have had elevated serum transaminases (Fig. 3A, B). Although bilirubin and albumin levels are typically normal, prothrombin (PT) and partial thromboplastin (PTT) times are frequently mildly elevated (Fig. 4). FibroScans, which measure liver tissue stiffness, can be abnormal in adult NPC1 subjects (Fig. 5). In addition, development of hepatocellular carcinoma has been reported in NPC1 patients [16-19] and developed in one subject followed at the NIH (Fig. 3C). We hypothesize that reduction of hepatic cholesterol storage through parenteral delivery of VTS-270 will be effective in reducing liver inflammation and restore normal hepatic function in NPC1 patients. The ultimate goal of this therapy is to prevent liver fibrosis and lower the risk of hepatocellular carcinoma.

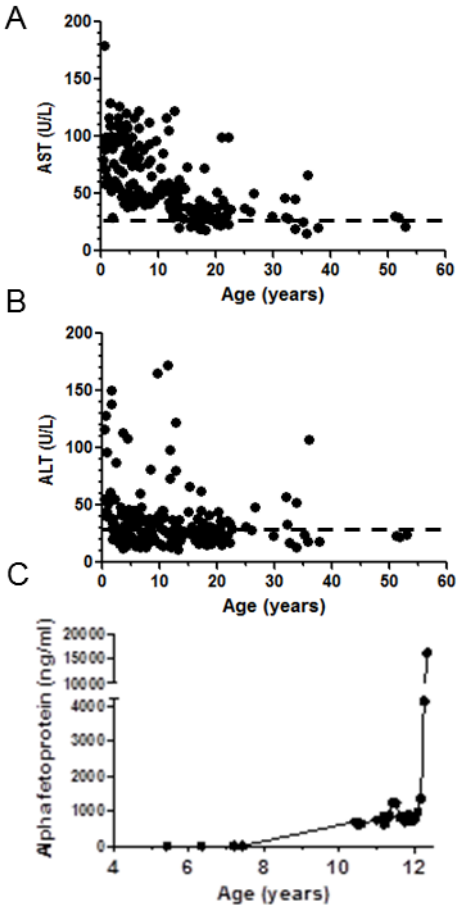

Figure 3. Serum transaminase (A,B) levels in NPC1 subjects from the NIH Natural History cohort. Dashed line indicates upper limit of normal. C) Serial α-fetoprotein levels in an NPC1 subject who developed hepatocellular

1.5 Route of Administration and Dose Selection Rationale

A Phase 1/2a trial of intrathecal VTS-270 has been completed (13-CH-0001; NCT01747135) and a multinational Phase 2b/3 trial (16-CH-0016; NCT02534844) evaluating the safety and efficacy of intrathecal VTS-270 for the treatment of the neurodegenerative aspects of NPC1 disease is in progress. In these trials, VTS-270 is being administered by lumbar intrathecal (IT) infusions since the drug is largely excluded from crossing the blood-brain barrier. Analysis of the 18-month Phase 1/2a trial data indicates that intrathecal therapy slows neurological disease progression (Fig. 1) [1]. However, direct CNS delivery, probably due to relatively low systemic exposure, appears unlikely to have an effect on peripheral disease.

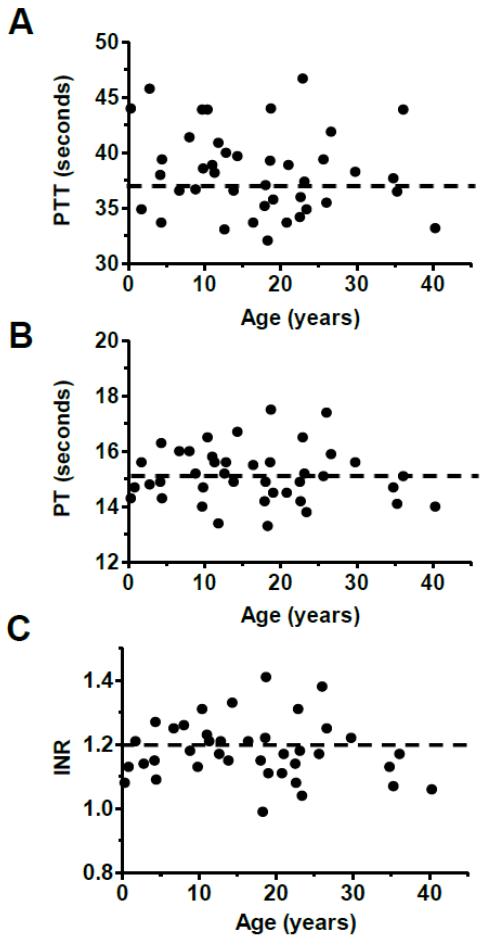

Figure 4. Assessment of liver synthetic function in NPC1 subjects for the NIH Natural History cohort. A) Partial thromboplastin time (PTT), B) Prothrombin time (PT) and C) International Normalized Ratio (INR) values in NPC1 subjects. Dashed lines denote upper limit of the normal range.

In the NPC1 cat model, subcutaneous administration of HPβCD 1000 mg/kg biweekly (11 treatments over 21 weeks) reduced serum ALT from approximately 6-fold elevated to 2-fold elevated [20]. This was accompanied by correction of the severe vacuolization of hepatocyte and Kupffer cell cytoplasm observed in untreated cats. In human NPC1 patients dosed under an individual IND, intravenous (IV) administration of HPβCD (2500 mg/kg biweekly) reduced by 2-fold plasma cholestane-3β,5α,6β-triol [21], an NPC1 disease-specific biomarker that monitors oxidizable free cholesterol in liver tissue [4]. Liver volume and AST were reduced in one of two subjects treated with 2500 mg/kg [32]. Toxicity appears to be limited, though at least one subject demonstrated pulmonary infiltrates at 2500 mg/kg [32]. IV HPβCD has been used under an emergency IND for acute liver failure in an NPC1 neonate. IV administration of a single dose of 1000 mg/kg HPβCD reduced the level of both cholestane-3β,5α,6β-triol and 7-ketocholesterol (another oxysterol elevated in NPC1 patients) by approximately 40 and 60%, respectively, within two days (personal communication, Dr. Gabrielle C. Geddes).

Taken together, the preclinical and human data suggest that VTS-270 administered by the IV route may be effective in reducing liver inflammation and injury and may mitigate severe long-term sequelae, such as cirrhosis and risk of hepatocellular carcinoma. For the proposed trial, IV doses of 500, 1000 and 1500 mg/kg are being planned, which are expected to be efficacious, while minimizing potential toxicity.

Outside of the neonatal period, neurological disease is the primary clinical problem in NPC1, thus as part of this protocol we may offer subjects the option of receiving intrathecal VTS-270 at a dose of 900 mg per month at the NIH Clinical Center. Monthly dosing of 900 mg is consistent with our Phase 1/2A study which studied doses between 50

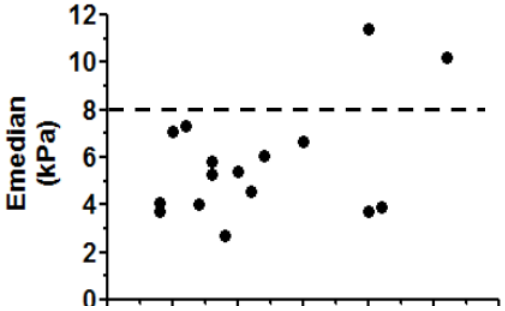

Figure 5. Liver FibroScans from NPC1 patients in the NIH Natural History cohort. Elasticity of liver tissue versus age is shown in NPC1 subjects from the NIH Natural History cohort. Normal is <7 kPa and >10 kPa is an indication to biopsy.

and 1200 mg [1]. The current Phase 2B/3 study is evaluating 900 mg administered every two weeks. Subjects in whom we initiate intrathecal VTS-270 therapy may be evaluated for exploratory outcome measures related to neurological disease.

2. Study Objectives

The primary objective of this study is to assess the safety and tolerability of intravenous VTS-270 in subjects with Niemann-Pick Disease, type C1.

The secondary objective of this study is to assess the potential efficacy of IV VTS-270 in treating chronic liver disease associated with Niemann-Pick Disease, type C1 as measured by reduction in plasma cholestane-3β,5α,6β-triol, an NPC1-specific pharmacodynamic biomarker.

Exploratory objectives will include liver enzyme levels, biomarkers, and assessment of liver size and stiffness.

An additional exploratory objective will be to obtain additional information related to potential neurological efficacy of intrathecal (IT) VTS-270. VTS-270 does not efficiently cross the blood-brain-barrier, thus the intravenous experimental therapy will not address the neurological aspects of NPC1. Based on the positive clinical results of our phase 1/2 data [1], we believe that offering IT therapy will be indicated in most cases; however, this will be optional. For participants electing to receive concurrent intrathecal VTS-270 therapy, neurological efficacy data obtained during their course of treatment will be of value. Therefore, we will collect data related to neurological progression under our Natural History protocol (06-CH-0186). Participation in these assessments is optional.

Specific Aims

Aim 1. To conduct a Phase 1/2a, open-label, parallel dose, randomized, single-center study to establish safety and tolerability of intravenous VTS-270 in treating liver disease associated with NPC1

Aim 2. To evaluate the potential clinical efficacy of intravenous VTS-270 in treating liver disease associated with NPC1 by measuring reduction in plasma cholestane-3β,5α,6β-triol levels

Aim 3. To evaluate the relationship between clinical response, as measured by serum transaminases, imaging biomarkers and exploratory research outcome measures

3. Subjects

3.1 Description of study population

Patients will be diagnosed as having NPC1 based on criteria specified in Section 3.4. Subjects will be recruited from ongoing NIH protocols and patient support organizations. For potential subjects for whom a definitive diagnosis is not available, the investigators may assist the primary care physician in making a diagnosis. Alternatively, clinical testing (such as mutation analysis) can be performed using the NICHD protocol for evaluation of patients with genetic disorders (PI: Perreault, 16-CH-0103). Potential subjects referred for the study may be screened by phone to make a preliminary determination of eligibility. After signing a screening consent, we may obtain standard liver chemistries to help determine chronicity of the liver disease prior to admission to the NIH Clinical Center. Due to the nature of this disease, this study will enroll minors and adults with variable degrees of cognitive impairment; in these cases, parents, guardians or legally authorized representatives will provide informed consent for participation in the study. No exclusions will be made based upon gender, race or ethnicity.

3.2 Accrual Ceiling and target number of evaluated subjects

Our goal is to have 15 subjects complete this study. The study will enroll into the treatment phase up to a maximum of 18 patients to account for potential subject withdrawal or discontinuation. The study may screen up to 30 individuals.

3.3 Subject replacement

Any usable data from withdrawn patients will be included in safety and efficacy evaluations. Patient withdrawn from the IV aspect of this protocol may be replaced.

3.4 Inclusion Criteria

1. Age ≥ 3 and ≤ 60 years old at time of enrollment

2. Diagnosis of NPC1 based upon <u>one of the following</u>:

A. Two *NPC1* mutations*

B. Biochemical Positive for NPC (oxysterol/bile acid** and sphingomyelinase levels consistent with a diagnosis of NPC) **and** one *NPC1* mutation*

**NPC1* mutations will be interpreted using standards established for the interpretation of sequence variants [33].

** Oxysterol/Bile Acid testing refers to cholestane-3β,5α,6β-triol [7, 8] or 3β,5α,6β-trihydroxycholanic acid and its glycine conjugate [34].

3. Evidence of chronic NPC1-related liver disease defined as one of the following (A, B or C):

A. Abnormal liver chemistries as defined by one of the following:

i. Plasma aspartate aminotransferase (AST) ≥ 1.5-times age-appropriate upper limit of normal
ii. Plasma aspartate aminotransferase (AST) ≥ 1.25-times age-appropriate upper limit of normal **and** plasma alanine aminotransferase (ALT) > 1.25-times age-appropriate upper limit of normal
iii. Plasma aspartate aminotransferase (AST) ≥ 1.25-times age-appropriate upper limit of normal and AST/ALT ratio ≥ 2.0

AND

Abnormal liver chemistries as defined above at least 8 weeks apart.

B. Abnormal Liver Ultrasound* defined as one of the following:

1. Intraparenchymal echogenic bands consistent with fibrosis

2. Abnormal liver echogenicity with AST or ALT above the upper limit of normal (applicable ranges referenced in previous inclusion criteria 3A).

3. Hepatomegaly with AST or ALT above the upper limit of normal (applicable ranges referenced in previous inclusion criteria 3A)..

To define hepatomegaly, we will use the suggested limit of normal of the longitudinal dimension of the right lobe of the

liver as published by Konus et al. [35]. These values are approximately 2 standard deviations above the mean. Please see table 1 for specific age dependent values.

C. Abnormal liver stiffness (FibroScan**) for age.

To define Liver Stiffness Measurement we will use the normal age dependent ranges published by Tokuhara et al. [36]. Values above the 95th centile will be considered abnormal. Age dependent abnormal values are provided in Table 2.

5. Ability to travel to the NIH Clinical Center repeatedly for evaluation and follow-up.

6. Willingness to discontinue all non-prescription supplements, except for an age appropriate multivitamin/mineral supplement.

7. Stable miglustat dose for 3 months prior to entry into the IV portion of the trial.

8. Women of reproductive age must be willing to use an effective method of contraception for the duration of the trial if sexually active.

9. Willingness to participate in all aspects of the IV trial

Table 1. Definition of hepatomegaly (adapted from [35])

Age Range (years)	Longitudinal Dimension of the Right Lobe (mm)
≥ 3 to < 5	115
≥ 5 to < 7	125
≥ 7 to < 9	130
≥ 9 to <11	135
≥ 11 to < 15	140
≥ 15	145

Table 2. Definition of increased Liver Stiffness Measurement

Age Range (years)	LSM (kPa)
≥ 3 to < 6	≥ 4.6

≥ 6 to < 12	≥ 6.1
≥ 12	≥ 7.9

*Ultrasound will be performed as a clinical scan without modification.
**Fibroscan will be performed as a clinical scan without modification.

Inclusion criteria testing may be obtained using our NPC1 natural history protocol or as part of this protocol prior to administration of drug. To establish chronicity, AST and ALT testing may be performed by an outside clinical laboratory prior to enrollment in this protocol.

3.5 Exclusion Criteria

1. Age <3 or > 60 years of age at time of enrollment in the trial.

2. Subjects who have received any form of parenteral cyclodextrin, an HDAC inhibitor, or an experimental therapy for NPC in the prior six months. Prior Intrathecal VTS-270 treatment is allowed per section 4.5.6.

3. History of hypersensitivity reactions to cyclodextrin or components of the formulation.

4. Pregnancy or breastfeeding. Females of childbearing potential unwilling to utilize a highly effective form of contraception (i.e., barrier method with spermicide, intrauterine device, steroidal contraceptive in conjunction with a barrier method, or abstinence if it is the patient's baseline preference) for the duration of the study and for 30 days after participation.

5. Any systemic infection at the time of enrollment.

6. Neutropenia, defined as an absolute neutrophil count (ANC) of less than 1,500 per microliter. Subjects with benign cyclic/ethnic neutropenia may be enrolled if not clinically symptomatic.

7. Thrombocytopenia defined as a platelet count less than 75,000 per microliter.

8. Established history of a chronic clotting or bleeding disorder.

9. Use of anticoagulants within 3 months of enrollment

10. Severe or acute liver disease as defined by one of the following:

    A. AST or ALT greater than 10-times age-appropriate upper limit of normal

B. Jaundice or right upper quadrant pain

C. INR >1.8

11. Individuals with AST and ALT greater than 4-times the age-appropriate upper limit of normal will be excluded if they have a positive NIH Clinical Center Viral Markers Hepatitis Screen (HBsAG, anti-HCV and Anti-HAV IgM). This screening test will not be obtained unless AST and ALT are elevated. An equivalent panel from another laboratory may be used if this elevation is noted on screening. Individuals excluded under this criterion may be rescreened after the acute pathology resolves (e.g. Hepatitis A infection).

12. Presence of anemia defined as two standard deviations below normal for age and gender.

13. Serum creatinine level greater than 1.5 times the age-appropriate upper limit of normal or for individuals ≥ 6 years of age an eGRF < 60 mL/min/1.73 m^2.

14. Hematuria on a single urinalysis, as defined by the American Urological Association (AUA) as five or more red blood cells per high-power field on microscopic evaluation of urinary sediment from a properly collected urinalysis specimen. The patient will not be excluded if two subsequent urine specimens are negative for hematuria as defined by the AUA.

15. Proteinuria (1+ protein on repeat urinalysis) unless evaluated and classified as benign.

16. Active pulmonary disease, oxygen requirement or clinically significant history of decreased blood oxygen saturation (SaO_2 <95% on room air), pulmonary therapy, daily use of a cough assist device or pulmonary vest, requiring active suction, or with a tracheostomy.

17. Patients with uncontrolled seizures per either of the criteria below.

a. Unstable frequency, type or duration of seizures. Quantified by a seizure log over one month prior to enrollment.

b. Subject requiring antiepileptic medication changes (other than dose adjustments for weight) in the month prior to enrollment.

18. Individuals receiving parenteral nutrition will be excluded.

19. Patients, who in the opinion of the investigators, are unable to comply with the protocol or have specific health concerns that would potentially increase the risk of participation.

Exclusion criteria testing may be obtained using our NPC1 natural history protocol or as part of this protocol prior to administration of drug.

3.5.1 Additional exclusion criteria for intrathecal VTS-270

1. Neurologically asymptomatic. Determination made by the investigators based on history, neurological exam and consultant input.
2. Suspected infection of the central nervous system
3. Spinal deformity that would impact the ability to perform a lumbar puncture
4. Skin infection in the lumbar region
5. Prior use of anticoagulants or a bleeding disorder with increased risk of clinical bleeding.
6. Patients unable to complete a behavioral audiological evaluation including pure-tone threshold assessment (500 Hz to 8000 Hz). In consultation with the medical monitor and audiologists, a sedated ABR may be utilized to monitor ototoxicity if the participant is being sedated to receive IT VTS-270.
7. Patients, who in the opinion of the investigators, are unable to comply with the protocol or have specific health concerns that would potentially increase the risk of participation.

3.5.2 Justification for exclusion of pregnant and lactating women

This protocol is a phase 1/2a study of an investigational drug. The potential risks of this drug to a fetus or exposure to a nursing infant are not known.

4. Study Design and Methods

4.1 Study Overview

The proposed trial will be a Phase 1/2a, open-label, randomized, parallel dose, single-center study of VTS-270 in subjects with NPC1 dosed monthly with IV VTS-270 for 12 administrations. The study will evaluate the feasibility, safety, tolerability, pharmacodynamic and disease-modifying activity of IV VTS-270 on visceral disease manifestations. Information obtained from this trial will be valuable in designing a future controlled trial to establish efficacy.

The primary outcome measure to monitor potential drug efficacy will be reduction in plasma cholestane-3β,5α,6β-triol, a cholesterol oxidation product that serves as a pharmacodynamic (PD) marker of the effect of the drug to reduce the oxidizable cholesterol pool in liver tissue.

This study will also evaluate the effect of intravenous VTS-270 on a series of disease-associated biomarkers, plasma liver enzyme levels (AST and ALT), liver size and liver stiffness.

Patients who have been screened for eligibility will be admitted to the NIH Clinical Center qualification assessments after written informed consent has been obtained. Patient screening may include obtaining serum liver tests including AST and ALT if this data is not available from our Natural History study (06-CH-0186). A telephone screening consent will be used. Only one parent/guardian signature will be required for the screening consent if the participant is not able to consent themselves. Telephone consent for this screening may be obtained by any investigator on this protocol.

To address neurological aspects of this disorder, this trial will include the option of monthly intrathecal VTS-270 administration. Individuals receiving intrathecal VTS-270 will be enrolled in our Natural History/Observational protocol (06-CH-0186) to monitor neurological aspects of the disease. Optional IT dosing will be discussed below (Section 4.5.6). If intrathecal VTS-270 therapy is initiated, IV dosing will be delayed until after at least three doses of IT VTS-270.

The first admission for IV VTS-270 administration will last approximately five days.
Baseline studies including liver/spleen ultrasound and liver FibroScan will be obtained. These baseline studies can occur to 35 days prior to the first IV administration. Subsequently the subject will be admitted on a monthly (4 ± 1 week) basis for IV drug administration.

A total of 12 IV doses will be given. The first IV dosing admission will be as an inpatient to facilitate post-dose monitoring. Subsequent admissions for drug infusion will typically use the 1NW day hospital. Follow-up liver/spleen ultrasound, liver FibroScan, and audiological evaluations will be obtained on the admission following the 6th dose. One month (4 ± 1 weeks) after the twelfth drug administration the subject will be admitted to the NIH CC for liver/spleen ultrasound, liver Fibroscan and audiological evaluation. Clinical and research laboratory and research testing will be performed at each admission.

4.1.1 Outline of protocol admissions and testing: Intravenous VTS-270

We plan to study 15 participants. To account for potential subject withdrawal or discontinuation, up to a maximum of 18 participants may be enrolled. Up to 30 individuals may be screened for this protocol. It is anticipated that this study will take three years to complete including a 2-year enrollment period and 12 months of IV dosing for each patient.

Study-related assessments will be conducted at the NIH Clinical Center and will include study admissions. The intravenous VTS-270 study will involve up to fourteen admissions during the one year of each subject's participation. Three additional admissions will occur if IT VTS-270 is provided. Admissions will be a combination of inpatient and day hospital.

The protocol includes "at home" interval safety testing involving phlebotomy and interval phone safety interviews.

IV VTS-270 administration timeline

Time	**Major Events**	**Admission Type***	**Length****
Screening/ Baseline	Enrollment and intravenous consent, Imaging evaluation 1st dose	Inpatient/Day Hospital	4-5 days
1-2 weeks	Safety labs	At home	-
1 month	2nd dose	Day Hospital	2
2	3rd dose	Day Hospital	2
3	4th dose	Day Hospital	2
4	5th dose	Day Hospital	2
5	6th dose	Day Hospital	2
6	Imaging evaluation 7th dose	Day Hospital	2-3
7	8th dose	Day Hospital	2
8	9th dose	Day Hospital	2
9	10th dose	Day Hospital	2
10	11th dose	Day Hospital	2
11	12th dose	Day Hospital	2
12	Imaging evaluation	Day Hospital	2-3

*May adjust as needed
**Approximate.

4.1.2 Outline of protocol admissions and testing: Intrathecal VTS-270

Given our data supporting the potential efficacy of intrathecal VTS-270 [1], participants will have the option of receiving monthly doses of IT VTS-270 concurrent with this protocol. To avoid confounding interpretation of adverse events due to either intrathecal or intravenous, intrathecal administration will be initiated at least three months prior to initiation of intravenous therapy.

Time	Major Events	Admission Type*	Length**
Screening/ Baseline	Intrathecal Consent Neurocognitive, gait and audiological testing Administration of first IT dose (IT1)	Inpatient	3-4 days
1	Second IT dose (IT2)	Outpatient	1-2
2	Third IT dose (IT3)	Outpatient	1-2

*May adjust as needed
**Approximate

IV admistration may be started 2 days after the third IT administration if participant is on a stable dose.

If for some reason a participant, in the opinion of the investigators, can no longer be safely started or continued on IV VTS-270 after intitiation of the IT therapy, Investigators will work to transfer the participant to an outside provider under an expanded access IND after an additional four IT doses. However, we can not assure participants that an outside provider can be identified.

If after starting IT VTS-270 the participant/guardians elect not to participate in or electively withdraw from the IV VTS-270 trial, IT VTS-270 administration under this protocol will be discontinued at that time. Investigators will work to transfer the participant to an outside provider that can provide IT VTS-270 under an expanded access IND. However, we can not assure participants that an outside provider can be identified.

For participants who complete the IV VTS-270 trial, IT therapy may be provided under this protocol up to IT18. Investigators will work to transfer the participant to an outside provider who will provide VTS-270 under an expanded access IND. However, we can not assure participants that an outside provider can be identified.

IT VTS-270 dosing will be as described in section 4.5.4. If a stable IT dose can not be established by IT6, participants will have the option of continuing with the IV VTS-270 only.

4.2 Recruitment and accrual

4.2.1 Recruitment Strategy

Participants will be recruited using several approaches. NPC1 patients currently or previously enrolled in one of our protocols may be contacted. We may also discuss this protocol with families that contact us. Information about this protocol will be distributed to the NPC patient community via patient support groups and posting on ClinicalTrials.gov. Due to our longstanding relationship with the NPC community, investigators associated with this protocol are frequently asked to provide research updates to the NPC1 community by family support groups. The family support organizations frequently suggest that parents contact us for

information about studies. In our experience guardian to guardian communication via social media frequently leads to self-referral. We also have families referred to us by physicians familiar with our prior work.

4.3.2 Anticipated accrual rate

We anticipate enrolling at least 5 subjects per year.

4.4 Subject Screening

Review of eligibility may be performed through chart review, written query or via telephone. Medical records may be requested. A screening log will be maintained indicating status.

Investigators may facilitate obtaining studies required for determining eligibility (e.g. NPC1 genotyping), obtain these studies under 06-CH-0186 if the potential participant is enrolled in that study or utilize the NICHD genetics evaluation protocol (16-CH-0016).

If not already available, serum liver tests may be obtained to establish chronicity of the liver disease 8 weeks or more prior to enrollment in this trial. A screening consent may be used in this case. This consent may be obtained by any member of the research team and may be done by telephone. Only one parent/guardian signature will be required on the screening consent.

No study procedures will be conducted under this protocol until after consent is obtained.

4.5 Study Procedures

4.5.1 Study Drug

Mallinckrodt, Inc. will provide the study drug. Parenteral and intrathecal VTS-270 will not be provided under this protocol after completion of this study. The study team may work with participants/guardians to facilitate a transition to an expanded access IND for intrathecal VTS-270 after completion of this study.

4.5.2 Prior and Concomitant Medications

Participants will be allowed to continue an age-appropriate multivitamin/mineral supplement, and other required medications as prescribed by their physicians. Miglustat dose will be held constant starting 3 months prior to entry into the IV portion of the trial and during the trial. All concomitant medications will be

recorded in the appropriate case report form (CRF). The use of other nonprescription supplements will be discontinued at least one month prior to enrollment in this trial. Prescription medications will be maintained at a constant dose level/regimen throughout the duration of the study, unless dose adjustment is clinically necessary, or the dose needs to be adjusted for weight. Such adjustments will be recorded in the patient's CRF.

Participants will be given the option of receiving intrathecal VTS-270 at a dose of 900 mg per month if previously receiving this or a higher dose. For naïve participants we will initiate dosing at 600 mg with escalation to 900 mg if the 600 mg dose is tolerated. Individuals already receiving VTS-270 at a dose lower than 900 mg may be dose escalated to 900 mg or stay at their prior dose level. IT dosing in this trial will be monthly in all cases.

This group of patients will undergo exploratory evaluations related to neurological aspects of NPC1 using protocol 06-CH-0186.

4.5.3 Randomization

Dose will be either 500, 1000 or 1500 mg/kg. Subjects will be randomized in blocks of three to one of these three doses. The randomization table will be produced prior to the start of the trial. Assignment to the treatment group will not be blinded.

4.5.4 Intravenous Dosing

VTS-270 will be administered intravenously to specifically target liver disease. Study subjects will be randomized in to one of 3 dosing regiments: 500, 1000, or 1500 mg/kg of intravenous VTS-270. Maximal dose will be 35, 70 or 105 gm, respectively, for the three dosing levels.

Dose levels and maximum dose for each cohort are:

		Dose	Maximum dose
Cohort 1	5 subjects	500 mg/kg	35 g administered over 2 hours
Cohort 2	5 subjects	1000 mg/kg	70 g administered over 4 hours
Cohort 3	5 subjects	1500 mg/kg	105 g administered over 6 hours

IV VTS-270 will be administered via peripheral IV at a rate of 250 mg/kg/hr.

For the initial administration of the drug the subject will remain in the clinical center for at least 24 hours. Vital signs (temperature, heart rate, respiratory rate, blood pressure and SaO_2) and standard neurological checks will be conducted every 30 ± 10 minutes during and then for the first two hours after drug

administration, at 4 and 6 hours post infusion, and then at least every 6 hours until 24 hours post infusion. Standard code cart with medications to address infusion reactions is available on the unit.

For subsequent doses, vital signs (temperature, heart rate, respiratory rate, blood pressure and SaO_2) and standard neurological checks will be conducted at least every 30 ± 10 minutes during the first two hours and then every 2 hours until complete. Standard code cart with medications to address infusion reactions is available on the unit.

The infusion site will be monitored for signs of inflammation/irritation.

4.5.5 Intravenous Dose and Rate Adjustments

Subjects who do not tolerate (Section 7.9) the 500 mg/kg dose will be withdrawn from the study.

Subjects who do not tolerate the 1000 mg/kg dose may have the dose decreased to 500 mg/kg.

Subjects who do not tolerate the 1500 mg/kg dose may have the dose decreased to 1000 or 500 mg/kg.

Subjects may be withdrawn for any Grade 3 AE (per NCI's CTCAE version 5.0) possibly or definitely related to study drug.

Subjects will be withdrawn for any Grade 4 toxicity, Grade 3 pulmonary complications or evidence of Grade 3 renal injury.

Subjects will be withdrawn if it is determined by the investigators in consultation with the IRB that the limit of safety or tolerability has been reached.

Rate may be decreased in 25 mg/kg/hr increments to 175 mg/kg/hr if required. The rate and reason for reduction will be recorded. Subject will be withdrawn if the 175 mg/kg rate is not tolerated.

4.5.6 Interim analysis of Intravenous Dose

An interim analysis will be performed after obtaining 4-month cholestane-3β,5α,6β-triol and safety data on six trial participants. These data will be used to propose rational changes in the dosing regimen if a lower dose levels appears to be ineffective or a higher level is less tolerated than an apparent effective lower dose.

4.5.7 Intrathecal VTS-270 Dosing and Dose Adjustments

1. Participants may elect to receive intrathecal VTS-270 in conjunction with this protocol. Intrathecal VTS-270 is not a requirement of participation in this study. If elected, IT VTS-270 must be started prior to receiving IV VTS-270.

2. For participants ≥ 4 years old, the IT VTS-270 dose will be initiated at 600 mg and then dose escalated, if tolerated, to 900 mg every 4 weeks ± 1 week. Individuals already receiving IT VTS-270 at a dose ≥ 900 mg may be started at 900 mg. Individuals already receiving an IT VTS-270 dose < 900 mg may be dose escalated to 900 mg or maintained on either 400 or 600 mg for the duration of the trial.

   For participants ≥ 3 and < 4 years old, the IT VTS-270 dose will be initiated at 200 mg and then dose escalated, if tolerated, to 400 mg every 4 weeks ± 1 week. Individuals already receiving a stable and tolerated dose of VTS-270 may be maintained at that dose up to a maximum of 900 mg.

3. Subjects (≥ 4 years old) who do not tolerate the 900 mg dose may have the dose decreased to 600 mg. Subjects who do not tolerate the 600 mg dose may have the dose decreased to 400 mg. Intrathecal VTS-270 will be discontinued in subjects who do not tolerate 400 mg. They may continue, if tolerated, to receive IV VTS-270. The reason for the dose reduction will be recorded. Once reduced, doses will not be increased for the duration of the study.

   Subjects (≥ 3 and < 4 years old) who do not tolerate the 400 mg dose may have the dose decreased to 200 mg. Intrathecal VTS-270 will be discontinued in subjects who do not tolerate the 200 mg dose. The reason for the dose reduction will be recorded. Once reduced, doses will not be increased for the duration of the study.

4. The intrathecal dose must be stable for two doses prior to initiation of the IV study. For VTS-270 naïve participants, the IV study may be initiated 2 days after the second stable IT dose.

5. If the first IV drug administration is performed on the same visit as the third IT administration, then it may be administered 2 days after the IT

administration. If the first IV drug administration is performed on another visit, the first intrathecal dose will not be administered until ≥ 18 hours post IV infusion.

6. IT administration can be performed concurrently with IV administration after the first IV administration if the IV dose has not been changed. If a participant is receiving a new IV dose, the intrathecal dose will not be administered until ≥ 18 hours post IV infusion.

7. Subjects already receiving IT VTS-270 under another mechanism may enroll in this trial. Dose and interval will be 900 mg monthly. If the subject is already on a dose lower than 900 mg due to documented intolerance, then they may be enrolled into this study at a dose of either 600 or 400 mg. Dosing interval will be monthly irrespective of the prior dosing interval. If the dose is not escalated, the dose may be considered stable based upon review of the patients history.

4.6 Assessments, Procedures and Testing

Baseline and timing in this section is relative to the initiation of peripheral VTS-270 therapy.

For 6 and 12-month assessment 6 ± 1 and 12 ± 1.5 months is acceptable.

For testing performed monthly, ± 1 week is acceptable.

4.6.1 Medical History and Physical/Neurological Examinations

A medical history will be obtained, and a physical exam will be conducted after admission to the NIH Clinical Center and enrollment into the study. This will ensure that the patient's medical health is adequate to participate in this study. An interval history and a physical exam will be obtained on all subsequent admissions.

Anthropomorphic measures including weight and height will be obtained with each admission. Head circumference will be obtained on the initial visit.

Physical and neurological examinations will be obtained. Medical evaluations may include videotaping of neurological assessments. Recordings may be sent to other physicians in an effort to develop rating systems. Although the patients'

names will not be provided, the video recording may include the face or other identifiable features.

4.6.2 NPC1 Neurological Severity Score

The NPC1 Neurological Severity Scale [4] consists of clinical signs and symptoms in nine major domains (scored 0 to 5: ambulation, cognition, eye movement, fine motor, hearing, memory, seizures, speech, and swallowing) and eight minor domains (scored 0 to 2: auditory brainstem response, behavior, gelastic cataplexy, hyperreflexia, incontinence, narcolepsy, psychiatric, and respiratory problems). Subjects will be evaluated using this scale at baseline, 6 and 12 months.

4.6.3 Pulmonary Function Assessment

A baseline CXR will be obtained prior to the first administration of the study drug**.** Pulmonary function testing will be obtained at baseline and 12 months. CXR will only be repeated if clinically indicated. Assessment will consist of PFT (≥ 5 yo) or impulse oscillometer (< 5 yo) and 6-minute walk test. Pulmonary functional assessment may be performed at anytime during the study if clinically indicated.

4.6.4 Liver Enzyme Assessment

Plasma AST and ALT will be obtained each visit. Total and direct bilirubin, gamma glutamyl transferase (GGT) and alkaline phosphatase will be measured.

4.6.5 Abdominal Ultrasound

An abdominal ultrasound exam will be conducted at baseline, 6 and 12 months to determine liver and spleen volume.

4.6.6 Liver FibroScan

A liver FibroScan will be obtained at baseline, 6 and 12 months.

4.6.7 Audiological Evaluation.

A behavioral audiological evaluation will be obtained at baseline, 6 and 12 months relative to IT VTS-270. Additional audiological evaluations may be obtained if clinically indicated.

4.6.8 Clinical Laboratory Tests

Clinical laboratory testing will be conducted by the NIH Department of Laboratory Medicine.

4.6.8.1 Hematology/Chemistry

Fasting blood samples for the clinical laboratory tests will be collected by a qualified person using either indwelling catheter or by venipuncture.

Testing will include the following:

Hematology: complete blood count (CBC) with differential and platelet count
Coagulation: prothrombin time (PT) and partial thromboplastin time (PTT)
Clinical chemistry: electrolytes, fasting glucose, blood urea nitrogen (BUN), creatinine, AST, ALT, GGT, alkaline phosphatase, bilirubin (direct and total), albumin, calcium, magnesium, phosphorus, and CK.

eGFR will be determined using the Schwarz method to monitor renal function.

This testing will occur on each admission.

In addition to the above, serum antiepileptic drug levels and other clinically indicated laboratory testing will be obtained as necessary in applicable subjects.

4.6.8.2 Urinalysis

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity and microscopic analysis. This testing will occur on each admission.

4.6.8.3 Pregnancy Testing

All female subjects ≥10 years old or menstruating will have either a serum or urine pregnancy test performed prior to drug administration or study related procedures for all admissions. Guardians will be informed of a positive test. Investigators will assist if needed in identifying appropriate primary care and pregnancy outcome will be ascertained.

4.6.10 Research Laboratory Testing

4.6.10.1 Plasma and Serum

Plasma and serum will be collected under standardized conditions for biomarker analysis. Testing may be performed in clinical or research laboratories.
Research testing may be prioritized if there is an issue of blood limits. Research testing may include, but is not limited to the following:

Markers of cholesterol homeostasis (Baseline, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 months)

1. Plasma lipid panel (Cholesterol, Triglycerides, HDL cholesterol and LDL cholesterol)
2. Plasma lathosterol
3. Cholestane-3β,5α,6β-triol
4. Plasma oxysterol profile (4β-HC, 7-KC, 24-HC, 27-HC)
5. Lipoprotein analysis (NMR)

Plasma lipidomics (Baseline, 6, 12 months)

1. Sphingolipids: sphingoid bases, ceramides, glucosylceramides, lactosylceramides, gangliosides
2. Lysosphingolipids: lyso-sphingomyelin, and lyso-SM 509

Biomarkers of inflammation (Baseline, 2, 4, 6, 8, 10 and 12 months)
Such as LGAL3, cathepsin D, lysozyme, cytokines

Plasma bile acids (Baseline, 6, 12 months)

Alpha-fetoprotein (Baseline, 6, 12 months)
Markers of liver pathology (Baseline, 2, 4, 6, 8, 10 and 12 months)
Such as Hyaluronic Acid, TIMP1 and P3NP

4.6.10.2 Peripheral Mononuclear Cells

Blood may be collected for isolation of peripheral mononuclear cells (Baseline, 6, 12 months). Cells may be used to characterize expression of genes associated with cholesterol homeostasis or for lipidomics.

4.6.11 Assessments related to intrathecal VTS-270 administration

These assessments are optional and are components of our Natural History protocol (06-CH-0186). These evaluations include:

1. Motor function and gait analysis (every 6 ± 1 months)
    a. Gait analysis
    b. Balance testing
    c. Motion analysis of Finger-nose-finger test
2. Occupational therapy assessment (every 3 ± 1 months)
    a. Dynometer Grip Strength Assessment
    b. 9-hole Peg Test
    c. Jebsen-Taylor Hand Function Test
3. Timed Up and Go (every 3 ± 1 months)
4. Neurocognitive evaluation (every 6 ± 1 month)

4. Speech and swallow evaluation (every 6 ± 1 month)

4.7 End of participation

Parenteral and intrathecal VTS-270 will not be provided under this protocol after completion of this study. The study team may work with participants/guardians to facilitate a transition to an expanded access IND for intrathecal VTS-270 after completion of this study. Participants may continue to be seen by our research team at the NIH Clinical Center if enrolled in our Natural History study (06-CH-0186).

See section 8.4 with respect to patient withdrawal.

Participants will have access to all clinical tests and evaluations via the patient portal or copies of the medical record.

Research results will be shared in aggregate with the NPC1 patient and research community at conferences and ultimately via publication.

5. Management of Data and Samples

5.1 Biomaterial Storage and Use

Blood (serum and plasma) and urine will be collected as part of this protocol. CSF may be collected in subjects that are receiving IT VTS-270. Samples will be maintained under standard conditions in the NICHD biorepository. Coded samples may be sent to collaborators at either the NIH or other institutes. Material transfer agreements will be obtained when applicable per NIH policy. Biomaterial and data collected as part of this study may be used for future research related to Niemann-Pick disease. Coded or anonymized biomaterial and data collected as part of this study may be used for other projects specifically approved by an Institutional Review Board. Priority will go to studies related to Niemann-Pick disease.

Loss or destruction of specimens will be reported to the IRB.

At the conclusion of this study, biospecimens will be transferred to our ongoing Natural History protocol (06-CH-0186).

5.2. Genomic Data Sharing: Not Applicable

5.3 Data sharing

Data and samples may be shared with collaborating laboratories at NIH or outside of NIH or submitted to NIH-designated repositories and databases. Repositories receiving data or samples from this protocol may be open-access or restricted access.

Samples and data will be stripped of identifiers and may be coded ("de-identified") or unlinked from an identifying code ("anonymized"). When coded data is shared, the key to the code will not be provided to collaborators but will remain at NIH. Submissions to NIH-sponsored or supported databases and repositories will be reported at the time of Continuing Review. Submission to non-NIH sponsored or supported databases and repositories will be submitted for prospective IRB approval.

Required approvals from the collaborating institution will be obtained and materials will be shipped in accordance with NIH and federal regulations.

Our research data sharing policy for clinical studies is attached.

Deidentified data may be provided to Mallinckrodt to support development or regulatory approval of this drug. Deidentified data may be provided to another entity under a CRADA if Mallinckrodt elects to not pursue regulatory approval of VTS-270 per the provisions of the existing CRADA.

5.4 Data Handling and Record Keeping

5.4.1 Electronic Data

The protocol and associated data will be stored in the NICHD Clinical Trials Database (CTDB). The CTDB is a 21 CFR Part 11 compliant web-based application that supports flexible data capture, and reporting.

5.4.2 Case Report Form Completion

CRFs will be completed for each study patient. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the patient's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

The Investigator will maintain copies of the CRFs at the study site. For patients who discontinue or terminate from the study, the CRFs will be completed as much as possible, and the reason for the discontinuance or termination clearly and concisely specified on the appropriate CRF.

In addition, electronic data capture will be used for the study. History, physical examination, clinical chemistry laboratory values, and procedure records will be documented in clinical research information system (CRIS) by the medical care team. Completed electronic CRFs are to be signed off by the Investigator or his/her designee

5.4.3 Retention of Study Records

The Investigator will maintain all study records according to ICH/GCP guidelines and applicable regulatory requirements. Records will be retained for at least two years after the last marketing application approval and until there are no pending or contemplated marketing applications or two years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. If a custodial change occurs, it must be documented.

5.4.4 Direct access to source data

The Investigators will permit trial-related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.), in addition to CRFs.

5.4.5 Publication Policy

All information concerning use of VTS-270 in the context of this trial is considered confidential and shall remain the property of the NIH. In accordance with NIH policy, data will be shared outside of the consortium group principally through publications and presentations at scientific conferences. Publications reporting the results of this trial will be submitted in a timely way. Data will be made available to Mallinckrodt under a Cooperative Research Agreement or similar mechanism. There are no anticipated delays or impediments to free publication of these results regardless of the outcome.

5.4.6 Return of results and community engagement

Participants will have access to all clinical testing/evaluations through the NIH Clinical Center Portal. Protocol status is reviewed with participating families. Research results will be presented to the NPC1 disease community via presentations or updates to the family support groups. Copies of publications related to this research will also be made available to the family support groups.

The trial will be registered on ClinicalTrials.gov and results will be posted per FDAAA requirements.

Information about this trial will be provided to families participating in our NPC1 Natural History Protocol, distributed to family support groups and provided to medical providers or diagnostic laboratories that see NPC1 patients.

6. Additional Considerations

6.1 Research with investigational drugs or devices

VTS-270 is an investigational drug. This study requires an IND. VTS-270 will be provided by Mallinckrodt to develop VTS-270 for the treatment of NPC and will be stored in the NIH pharmacy.

6.2 Gene therapy

Not applicable.

6.3 FDA Consideration

Subjects currently enrolled under current IND 142671, currently receiving intrathecal adrabetadex appear to be benefiting from adrabetadex. Guardians of enrolled subjects perceive benefit of the drug that outweighs the risks, and they previously elected to continue the optional intrathecal administration through the end of this study when Mallinckrodt initially made the decision to discontinue their development program based on Phase 2/3 trials results. In enrolled participants, assessment of disease progression using the NPC Neurological Severity Scale and clinical assessment by individuals experienced with NPC are consistent with less than expected neurological disease progression.

Both participants and their legally authorized representatives have been informed and re-consented with the information received from Mallinckrodt. They also understand the risks associated with adrabetadex, including hearing loss, and understand that Mallinckrodt has reported no significant difference between patients treated with adrabetadex and sham-treated patients on any efficacy measures in their randomized, controlled trial. Families of the two participants are making arrangements to continue in the Rush University Expanded Access Program due to this perceived benefit.

At this time, both patients have already completed the phase of the study in which they would have experienced the hearing loss side effects of the study drug that were identified by Mallinckrodt as contributing to the negative risk-benefit ratio. Once both patients complete the optional IT portion of this study, we will be closing this study.

7. Risks and Discomforts

Efforts will be made to reduce physical and psychological stress by carefully explaining the study's procedures to the individual patients. Except when the patients are sedated by anesthesiology, guardians can elect to be present. Individual procedures and associated personal risks are briefly described below.

7.1 Medical Evaluations

There are no significant risks associated with the physical, neurological, and neuropsychiatric examinations. Multiple independent evaluations may be stressful to a child or an impaired patient. Clinical photographs or video may be obtained, and these could potentially be embarrassing to some patients.

7.2. Risk of Intravenous VTS-270

The risks of intravenous VTS-270 are not known. Animal studies and human experience with HPβCD and VTS-270 to date suggest that this can be done relatively safely; however, a major purpose of this study is to determine safety and tolerability of intravenous VTS-270 in NPC1 patients.

IV administration of an experimental drug could have untoward consequences including permanent disability or death.

Known toxic effects from the cat disease model include acute respiratory distress and death, and apparent irreversible deafness:

- Cats receiving 8,000 mg/kg HP-β-CD by subcutaneous injection developed acute respiratory distress and died due to this complication.
- Cats receiving multiple subcutaneous doses of 4,000 mg/kg or a single subcutaneous dose of 8,000 mg/kg HP-β-CD developed apparent irreversible deafness [37].
- A majority of mice receiving a single 8000 mg/kg subcutaneous dose of HP-β-CD had hearing loss due to loss of outer hair cells [38]. However, chronic dosing at 4000 mg/kg showed an initial hearing loss that subsequently recovered suggesting that homeostatic mechanisms could adjust to the lower dosing.
- Pulmonary toxicity has been reported in young pigs receiving IV HP-β-CD infusions [39]. Infusion of 1 g/kg of 40% HP-β-CD in normal saline over 40 minutes resulted in cardiovascular instability. Five infusions over two weeks of 0.25-0.5 g/kg over 40 minutes resulted in inflammatory pulmonary changes.

No adverse events related to pulmonary function have been reported for the children receiving IV or IT HPβCD under individual use INDs cited in the initial IND (IND 113273). The investigators are not aware of any pulmonary adverse events being reported in the eight other individuals receiving IV HPβCD under

expanded access INDs in the United States. Those individuals are typically receiving 2500 mg/kg HPβCD every week. Individuals in the US are receiving Kleptose HPB, from which VTS-270 is derived. Matasuo et al [32] reported transient diffuse pulmonary infiltrates and fever following infusions of IV HPβCD after 23 months of therapy. These resolved with prednisolone and antihistamine pretreatment and interpreted by the authors as an infusion related immunological reaction. The adverse pulmonary events appear to be related to high peripheral dosing. The HPβCD used by Matasuo et al is not the same preparation as VTS-270.

While an allergic or anaphylactic reaction to VTS-270 is unlikely, the first drug administration at each dose level will take place in a NIH Clinical Research Center inpatient unit; in order to closely monitor the patient for acute adverse effects including anaphylactic response to VTS-270. Nursing and medical staff are trained in Code Blue procedures as well as Advanced Life Support, and many staff members are trained in Pediatric Advanced Life Support. Emergency resuscitation carts (Code Carts) are in place on every Patient Care Unit.

Exact doses for emergency resuscitation drugs for pediatric patients (defined as less than 18 years of age) who weigh less than 50 kg are calculated immediately upon each admission and recorded on the Pediatric Emergency Drug Sheet (PEDS). These include medications necessary for managing anaphylactic reactions (epinephrine, diphenhydramine and hydrocortisone). A copy of this document is kept on the patient's medical record as well as on the Code Cart on the Patient Care Unit for the duration of the admission. The Clinical Center Code Team includes a pediatric physician.

IV VTS-270 will be administered by peripheral IV. It is possible that this will result in irritation, inflammation or pain at the site of administration. We will monitor the infusion site for infustion related problems.

7.3 Urine Collection and Pregnancy Testing

There are no to minimal risks involved with a urine pregnancy test. A blood-based pregnancy test may be substituted. The patient will not be eligible to participate in the study if she is pregnant. A urine cup, toilet hat, or a urine bag to collect urine will be used. Patients will not be catheterized for this study. This collection may be inconvenient and there may be mild discomfort associated with bagging. For cognitively impaired adults, guardians will be informed of a positive test. A serum pregnancy test may be conducted in lieu of a urine pregnancy test. The consent document will inform sexually active subjects that they should practice effective birth control during the duration of this study.

7.4 Phlebotomy

Phlebotomy is a risk/discomfort of this study. An anesthetic cream such as EMLA is an option. Infection and bruising are possible at the site of the blood draw. The amount of blood to be drawn will not exceed the NIH CC guidelines of for children or adults of 5 or 10.5 ml/kg per day, respectively. Nor will we exceed the 8-week limit of 9.5 ml/kg or 550 ml for children or adults, respectively. Nursing staff will monitor blood-drawing volumes. If blood limits are an issue, testing will be prioritized by the investigators. Safety laboratory tests will take priority over investigational testing. Not obtaining a test due to blood limit prioritization will not be considered a protocol deviation. If a patient is concurrently enrolled in another protocol, the total blood volume collected across all protocols for research will not exceed the above limit.

7.5 Audiological Evaluation

For the hearing test the patient will wear headphones or soft foam earplugs. Tones and words that vary in loudness will be played over the earphones and the patient will be asked to respond to the sounds. This testing lasts approximately 15 minutes and involves minimal discomfort. Acoustic reflex measurement allows the audiologist to further examine the integrity of the acoustic reflex arc, which relies on functional integrity of the middle ear system, inner ear, seventh and eighth cranial nerves and auditory pathways in the lower brainstem. For this test, very brief, somewhat loud tones are presented to each ear. In a normal-hearing ear, the stapedius muscle in the middle ear contracts in response to loud sounds presented at levels of about 70-100 dB HL (decibels hearing level). In this test, the audiologist presents tones at these levels and determines whether there is an acoustic reflex and what level of sound is required to produce the reflex. This is a standard audiologic test. The audiologic evaluation will also include measurement of auditory evoked potentials. For this testing the patients will wear either headphones or soft, foam earplugs. Four electrodes will be taped to the patient's head and the electrical response to sound will be recorded. This testing lasts approximately 30 minutes. This testing involves minimal discomfort and no risk.

7.6 Sedation

Sedation for study procedures may be performed at the discretion of the research team in consultation with the patient/guardians and anesthesiology. The medical and anesthesia clearance may determine that the patient is not fit for sedation during study procedures due to pre-existing medical conditions that would cause this elective procedure to be riskier. If that is the case, and sedation is necessary, the patient will be excluded from the study.

The major risk associated with sedation is respiratory collapse. To minimize this possible complication, sedation will be performed by an NIH Clinical Center

anesthesiologist. Facilities for maintenance of a patient airway, artificial ventilation, and circulatory resuscitation will be immediately available and ready for use. The anesthesiologist will also select the anesthetic agent used based on their clinical judgment. Criteria used in making this judgment include patient age, size, history of reflux, history of difficult airway management, and overall medical status. Another risk of sedation is aspiration. Intubation decreases the risk of aspiration and may be used if in the opinion of the anesthesiologist that it is indicated. Death is a rare complication of sedation when performed by a licensed anesthesiologist under controlled conditions.

Exposure to repeated and prolonged anesthesia in young children may affect neurocognitive development. Sedation in young children will be assessed on an individual basis, and efforts made to consolidate evaluations and procedures optimally done under sedations to minimize the anesthesia time.

7.7 Radiation Exposure

Radiation exposure due to participation in this study comes from the baseline Chest X-ray. The estimated total body exposure is 0.007 cSv.

This exposure is below the NIH Radiation Safety committee guidelines of 5 cSv per year for adults. This exposure is below the NIH Radiation Safety committee guidelines of 0.5 cSv per year for individuals under 18 years of age. The risk of this radiation exposure has to be weighed against the severity of this disease and the potential direct benefit of this therapy.

Female participants will be asked to inform any study coordinators, nurses and the x-ray technologist if there is any possibility that they are pregnant.

The average person in the US receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, cosmic radiation, and the earth's air and soil. If the patient/guardian would like more information about radiation, he/she may ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

The source will be a chest X-ray that will be obtained on the first admission and this will serve as a baseline study should pulmonary symptoms be observed during the study.

There is no discomfort and minimal exposure to radiation when obtaining a CXR. The CXR is one of the lowest radiation exposure medical examinations performed today. The radiation dose from this CXR is about 0.007 cSv.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer. The

participant/guardian will inform one of the doctors if he/she has had any radiation exposure in the past year, either from other research studies or from medical tests or care, so the doctors can make sure that the subject will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into the subject's body. If the participant is pregnant or breast feeding, she may not participate in this research study. It is best to avoid radiation exposure to unborn or nursing children since they are more sensitive to radiation than adults.

7.8 Liver/Spleen Ultrasound and Liver Fibroscan

The risks of an abdominal ultrasound or transient elastography (Fibroscan) are limited to mild discomfort of the technicians pressing the probe against the abdominal wall.

7.9 Future Research and Other Testing

Other blood, cellular, urine or CSF biomarkers may be assessed. At the discretion of the investigator, blood, urine, and CSF may be collected and saved for future research. The blood, urine, CSF, and derivatives thereof (e.g., exosomes, peripheral B-cells, ribonucleic acid (RNA) or deoxyribonucleic acid (DNA)), collected under this protocol, can be stored for future research not specifically outlined in this protocol. Such research could involve, but is not limited to, proteomic, genomic, biochemical, metabolomic, and molecular analysis of these samples. Data collected under this protocol may be used for future research. Future research using these samples and data will relate to Niemann-Pick disease or other projects specifically approved by an Institutional Review Board. Priority will go to studies related to Niemann-Pick disease. This research may occur at the NIH or at outside laboratories. If sent to outside laboratories samples will be coded and patient identifiers will be removed. If biospecimens are sent to a clinical laboratory for testing, identifiers will not be removed, and the result will become part of the NIH medical record. For patients also enrolled in the ongoing Natural History Study (06-CH-0186), biospecimens collected during admissions for this protocol can be used for research specified in that protocol. Sample volume safety limits will take into account both protocols.

Data collected under this protocol may be used in future studies.

Data collected under this protocol and the Natural History study may be exchanged if a participant is enrolled in both studies. Upon closure of this protocol, all data and biomaterials will transfer to 06-CH-0186.

7.10 Lumbar Puncture

There are several potential risks associated with an LP. About a third of adults report a headache after a LP. The frequency is lower in children. This can be made less by lying flat in bed and taking medications such as Tylenol. Although rare, bleeding may occur near the puncture site or in the deep tissue around it. Which may cause; pain, loss of sensation in the feet, loss of bowel or bladder control, and numbness, cramping, or weakness in the arms, hands, or legs. There is a risk of causing a serious infection in the CSF known as meningitis. To prevent this, the LP will be done using sterile techniques and instruments. A rare but serious complication of a LP, if it is done when the pressure inside the head is higher than normal (such as when a brain tumor is present), is known as medullary herniation which can result in death. Increased intracranial pressure is very unlikely to be present. The LP will not be done if there are any clinical indications of increased intracranial pressure, a skin infection in the lower back area, or bone malformation of the lower back (including severe scoliosis) which would make a LP difficult. We will do the LP monthly for drug administration. CSF will be collected and saved each time we do an LP. The LP will be performed under sedation if the participant is unable to cooperate with the procedure while awake.

8. Subject Safety Monitoring

8.1 Monitoring of Adverse Event Data

The investigators have primary responsibility for the ongoing monitoring of adverse events. Adverse events will be summarized and reported to the NICHD IRB. This study will use a medical monitor. The study is not blinded, of relatively short duration and involves a small number of subjects that can be adequately assessed through simple comparison, thus a DSMC is not required.

8.2 Review of Safety and Tolerability

The evaluation of a dose for an individual will be reviewed by the Principal Investigator and research team. See Table 1.

8.2.1 Tolerability Determinations

Adverse events will be assessed using CTCAE version 5.0. Safety and tolerability of VTS-270 will be determined as presented in table 1 except for respiratory and audiological complications.

High frequency hearing loss is a known symptom of NPC1 and ototoxicity is a known complication of IT VTS-270 administration. Audiological changes will not be considered to be related to IV VTS-270 in subjects receiving IT VTS-270

unless the changes exceed or are qualitatively different than those expected based upon our experience with IT VTS-270.

Post-dose fatigue and ataxia is a known complication of IT VTS-270 administration. These symptoms will not be considered related to IV VTS-270 in subjects receiving IT VTS-270 unless they are qualitatively different than those expected for the individual.

8.2.1 Review of Respiratory Compromise

The study will be discontinued if two subjects demonstrate respiratory compromise associated with drug infusion at 500 mg/kg dose. If two subjects demonstrate respiratory compromise associated with drug infusion in cohort three (1500 mg/kg group), dosing for all subjects in this cohort will be decreased to 1000 mg/kg/d. If two subjects demonstrate respiratory compromise associated with drug infusion in cohort two (1000 mg/kg), consideration will be given to reducing dosing for cohorts two and three depending upon the total trial experience. This latter decision will be made in consultation with the FDA and IRB.

We will consider respiratory compromise to be one of the following:

1. Sustained tachypnea for 30 minutes or dyspnea during drug infusion or within 2 hours post infusion that is likely related to drug administration. The individual subject will be withdrawn, or the dose decreased.

2. Decreased SaO_2 (<90%) during drug infusion or within 2 hours post infusion that is likely related to drug administration. The individual subject will be withdrawn, or the dose decreased.

3. Repeat CXR demonstrating pulmonary infiltrates likely related to drug administration. If the etiology of pulmonary infiltrates is not known, the dose may be repeated and a subsequent CXR obtained. If the subsequent CXR demonstrates increased pulmonary infiltrates, subject will be withdrawn, or the dose decreased.

8.2.2 Review of High Frequency Hearing Loss

High frequency hearing loss is considered an expected complication of VTS-270 administration. Evaluation will be confounded by potential concomitant administration of intrathecal VTS-270. No changes to this protocol will be made unless the degree of hearing loss exceeds that typically observed in our Phase 1/2a intrathecal HP-β-CD trial (13-CH-0001).

8.3 Data Safety Monitoring Board

This protocol does not meet the criteria as outlined in the NIH HRPP SOP 17 for data to be submitted to a data safety monitoring committee. The IRB will be consulted concerning dose reductions and subject withdrawal.

8.4 Withdrawal of Patients from the Study

Participants can withdraw from the study at any time for any reason. Patients/guardians/parents will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care. However, to receive care at the NIH CC, patients must be enrolled on a research protocol. The Natural History Study provides an alternative to this protocol. Patients who are withdrawn from the study either by their choice or investigator action will be notified and provided with recommended follow-up instructions in writing.

Patients may be withdrawn from the study for any of the following reasons:

Patient/parent/guardian request

Patient/parent/guardian is unwilling or unable to comply with the protocol

Medical reason, at the discretion of the Investigators

Occurrence of the following:

a. any Grade 3 AE (per NCI's CTCAE) possibly or definitely related to study drug
b. any Grade 4 toxicity
c. any subject with Grade 3 pulmonary complications or evidence of renal injury
d. determination that the limit of safety and/or tolerability has been reached

Table 1. Decision Table for Evaluating the Safety and Tolerability of IV VTS-270 in Individual Patients (respiratory and audiological excluded)

	Safety Profile of Individual Patient	Safety Decisions*
A	No AEs and no SAEs or Any number of CTCAE Grade 1 drug-related AEs; ≤ 1 CTCAE Grade 2 drug-related AE; or	Repeat the current dose
B	2 CTCAE Grade 2 drug-related AEs (or	Repeat the current dose, Study a lower dose (if applicable)
C	≥ 3 CTCAE Grade 2 drug-related AEs or ≥ 1 drug-related SAE	Study a lower dose, or withdraw the patient and Evaluate the risk/benefit profile for this dose for other patients
D	Any CTCAE Grade 3 drug related AE; Any CTCAE Grade 4 AE; Determination that the limit of safety and/or tolerability has been reached	Withdraw the patient and Evaluate the risk/benefit profile in other patients for the dose resulting in Grade 3 toxicity and Discontinue study if two patients develop the same Grade 3 toxicity or if any patient develops a Grade 4 toxicity

Guardians or consenting participant may request discontinuation of study medication. In this case although study treatment will cease immediately, end of study evaluations may be completed.

The reasons for patient withdrawal will be recorded in the patient's CRF.

For a withdrawal due to a safety issue, patients will be followed until the safety issue is resolved or returns to baseline level. Additionally, any appropriate referrals will be made as needed. Referrals may involve an institution other than the NIH CC.

Expenses due to research related injuries will be handled per NIH policy.

A participant may withdraw or be withdrawn from the IT VTS-270 aspect of this protocol and continue with the IV VTS-270 trial. Participants can not withdraw from the IV VTS-270 trial and continue to receive IT VTS-270. If investigators withdraw a participant from the IV VTS-270 trial due to a safety concern, the

patient may continue to receive monthly IT VTS-270 under this protocol for up to 15 months.

Any usable data from withdrawn patients will be included in safety and efficacy evaluations. Patient withdrawn from the IV aspect of this protocol may be replaced.

8.5 Discontinuation or Temporary Suspension of the Study

The Principal Investigator may terminate this study at any time for safety or administrative reasons. The Principal Investigator will terminate the study if the occurrence of AEs or other findings suggests an unacceptable risk to the health of the subjects. The study will be stopped if two subjects develop the same Grade 3 adverse event (unless related to disease progression of NPC), or if any patient that develops a Grade 4 adverse event, regardless of whether the event is determined to be related to the study drug (unless the AEs are of an accidental nature that could not be reasonably attributable to VTS-270 or related to disease progression of NPC).

9. Outcome Measures

9.1 Primary outcome measures

The primary clinical outcome measure for this trial will be to delineate safety and tolerability of intravenous VTS-270 in NPC1 participants. Adverse events, as delineated in section 8, will be used to determine safety and tolerability.

The primary biochemical outcome measure for this trial will be reduction of the plasma cholestane-3β,5α,6β-triol level (ng/ml).

9.2. Secondary outcome measures

The secondary clinical outcome measure for this trial will be reduced liver size (cm^3) or stiffness (kPa).

The secondary biochemical outcome measures for this trial will be reduction of serum transaminase levels (AST, ALT) or improved AST/ALT ratio. AST and ALT will be reported in U/L.

9.3. Exploratory outcome measures

Evaluation of potential biomarkers (Section 4.6.10) will be considered exploratory. Outcome measures related to IT administration are considered exploratory

10. Statistical Analysis Plan

The primary clinical outcome of this study is to assess the safety and tolerability of intravenous VTS-270 in subjects with Niemann-Pick Disease, type C1.

Assessment of safety and tolerability will be made by evaluation of summary statistics of adverse events and unanticipated problems. Adverse events and tolerability are defined in section 8 and will be summarized for each dose level.

We hypothesize that the total number of drug-related adverse events will not increase with dose level and we will not observe an increase in the number of a specific type of drug-related adverse event increase with dose level.

A dose will be considered tolerated if not more than one participant in a dose cohort requires either dose reduction or withdrawal from the protocol due to a drug-related issue.

The primary biochemical outcome of this study is to assess the potential efficacy of IV VTS-270 in treating chronic liver disease associated with Niemann-Pick Disease, type C1 as measured by reduction in plasma cholestane-3β,5α,6β-triol, an NPC1-specific pharmacodynamic biomarker.

Plasma cholestane-3β,5α,6β-triol, a biomarker that is elevated >97% of NPC1 subjects, is largely generated in the liver and therefore provides a biochemical measure of oxidizable lysosomal unesterified cholesterol in liver tissue (6, 20). We hypothesize that there will be a significant reduction in the last treated plasma cholestane-3β,5α,6β-triol concentration relative to baseline in each of the three dose cohorts.

Limited data is available to estimate the power of this study. The mean and standard deviation of plasma cholestane-3β,5α,6β-triol levels for 109 NPC1 patients and 89 controls were 80.3 ± 77 and 11.5 ± 3.3 ng/ml, respectively [7]. Due to the large variability among NPC1 patients, data will need to be normalized to the individuals baseline value. Serial plasma cholestane-3β,5α,6β-triol concentrations were measured in two NPC1 subjects over four years, during which period IV HP-β-CD treatment was initiated under an individual expanded use Investigation New Drug application. Baseline plasma cholestane-3β,5α,6β-triol concentrations for these two subjects were 60.7 and 53.5 ng/ml (normal <24.5 ng/ml). Plasma cholestane-3β,5α,6β-triol concentrations were reduced to

29.8 and 18.1 ng/ml after 8-12 months of IV HPβCD. Expressed as a percentage, mean reduction was 58.54 ± 10.79 percent.

	Power		
	90	**80**	**70**
90%	26	19	15
80%	7	5	4
70%	3	3	2

Setting the baseline at 100%, standard deviation at 11%, type one error at 0.05, for a two-tailed comparison the following table provides the number of subjects would be needed to achieve 90%, 80% and 70% power for a reduction of mean cholestane-3β,5α,6β-triol level to 90, 80 or 70 percent of baseline. Thus, we expect 80% power to detect a 20% reduction in mean cholestane-3β,5α,6β-triol levels using cohorts of 5 participants.

A major purpose of this trial is to obtain pilot data on potential clinical outcome measures and biomarkers to identify outcome measures that appear to respond to therapy and to inform power calculations for a subsequent trial focused on establishing therapeutic efficacy. Thus, secondary and exploratory outcome measures will be evaluated independently.

For group comparisons, such as comparing mean values of primary outcome measurements, the statistical significance of differences in mean values will be determined by a two-tailed single-factor ANOVA or Student's t test. To perform correlations, such as for comparison of primary/secondary outcome data with NIH severity scale values or clinical assessments, data will be analyzed using Pearson and Spearman correlations, as appropriate. A p value of 0.05 or less will be considered significant and p values between 0.05 and 0.10 will be considered a trend. Multiple comparisons will be corrected by appropriate post-hoc analysis.

11. Human Subjects Protection

11.1 Institutional Review Board

This protocol will be reviewed and approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Institutional Review Board (IRB). The IRB will meet all FDA requirements governing IRBs (Code of Federal Regulations (CFR), Title 21, Part 56).

11.2 Ethical Conduct of the Study

The investigator will conduct this study in compliance with Intramural NIH policy and FDA regulations.

11.3 Subject Selection

Patients will be diagnosed as having NPC1 based on criteria specified in Section 3.5. For potential subjects for whom a definitive diagnosis is not available, the primary care physician may assist in obtaining these results before enrolling the patient to this study.

Patients currently enrolled in the Natural History Study or individuals who have contacted the Investigator/Sponsor for information about NPC1 studies will be recruited for this study. Enrollment will be optional and electing not to enroll will not affect participation in the Natural History Study. Patients will be recruited through parent support organizations such as, but not limited, to National Niemann-Pick Disease Foundation (NNPDF), Ara Parseghian Medical Research Foundation (APMRF), Dana's Angels Research Trust (DART), Support of Accelerated Research for Niemann-Pick Type C (SOAR-NPC), and Fight NPC.

Information about this study will be posted on ClinicalTrials.gov.

11.3 Gender and Ethnic/Racial Background

Patients of any gender and ethnic/racial background will be eligible for this study. NPC1 is an autosomal recessive disorder, thus gender distribution is expected to be equal. NPC1 is a panethnic disorder, but several genetic isolates, due to founder effects, exist. These include Acadians in Nova Scotia, Hispanics in parts of Colorado and New Mexico, Costa Rico and a Bedouin Group in Israel. It is expected that the patient's ethnic/racial demographics will reflect disease demographics. The small size of this study could result in random skewing of the expected distribution for either gender or ethnic/racial background.

This is a study involving a small sample size from a limited patient population with a rare disease. Patients will be screened to determine if they are eligible to participate in the trial prior to enrollment. Selection bias will be minimized as much as possible by screening all interested NPC1 patients until the maximum accrual number has been met.

11.4 Research Involving Children

We will obtain written informed consent from the parents /guardian(s) who accompany the child to the NIH Clinical Center (CC). If possible, consent will be obtained from both parents/guardians. If the second parent is unable to attend the visit, the second parent will be consented via telephone or another electronic process. If the parents are divorced and share custody we will obtain consent from both parents. A witness to the consent process will be present at the location of the individual obtaining consent. The signed consent must be sent to

the research team by fax, post, or other forms of electronic transmission. According to 45 CFR 46. 408 when one parent is deceased, unknown, incompetent or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child, the permission of one parent suffices.

A screening consent may be used to allow for serum testing to establish chronicity of the liver disease. This may be obtained by telephone and obtained by any member of the research team. Only one parent/guardian signature will be required for the screening consent.

Due to the age range included in this study and possibility of cognitive impairment, obtaining assent may not be possible. The protocol will be explained in an age/cognitive appropriate manner. Verbal assent will be obtained from participants 7 years of age or older, unless precluded by the cognitive status of the child as assessed by the investigators. This verbal assent will be indicated on the consent document signature page by a parent or guardian.

For individuals who are capable of providing consent, we will re-consent at the first NIH visit after their 18th birthday. For cognitively impaired individuals who are unable to provide consent, we will consult the NIH Ability to Consent Assessment Team (ACAT) to determine if the guardian/parent may continue to provide consent.

For individuals who are not being followed on an active NIH protocol, data and biomaterials will be used consistent with the prior consent. This will also be applicable for the period of time between a subject turning 18 and a subsequent NIH admission.

With regards to the waiver of re-consent:

1. The research constitutes no more than minimal risk since it involves preexisting data and biomaterials.

2. The rights and welfare of the subjects will not be adversely affected.

3. Obtaining re-consent from individuals who no longer being followed at the NIH is not practical. Direct interaction and in some cases ethics consultation is required to establish competency with our patient population.

4. Whenever appropriate, subjects will be provided with any additional information that becomes available.

This study is consistent with 45 CFR 46.405. Specifically, the research involves greater than minimal risk but presents the prospect of direct benefit to the individual child involved in the research. Given that NPC1 is a progressive, lethal neurological disorder, with no FDA approved therapy, the risks in this protocol are commensurate with the disease process. The preclinical data in animal

models suggest that the risk is justified by the potential benefit should this drug prove to be efficacious in humans.

11.5 Research Involving Cognitively Impaired Patients

Because NPC1 is a progressive neurological disorder, some adult patients may not have the cognitive ability to provide informed consent. In this case, a parent or legal guardian may consent for the patient. If a patient presents to NIH and the ability to consent cannot be easily deduced, the NIH Ability to Consent Assessment Team (ACAT) will be consulted. The ACAT team will determine if the guardian/parent may provide consent.

Because a consenting patient could become cognitively impaired after providing initial informed consent, at the time of first admission, the Investigator will request that the patient enact a Durable Power of Attorney for Health Care Decisions to guide continuation should they become cognitively impaired.

Guardians of a cognitively impaired patient can withdraw consent for any part of this protocol at any time.

11.6 Other vulnerable subjects

11.6.1 Pregnant women

Pregnant women will be excluded due to use of an investigational drug and limited knowledge of the risks to the fetus.

11.6.2 Prisoners

Prisoners will not be excluded. Should this situation arise, the IRB, OHSRP and the NIH Ethics team will be consulted, and the protocol amended accordingly.

11.6.3 NIH Staff

We do not anticipate enrolling NIH staff but neither NIH staff nor their dependents will be excluded. Exclusion would not be appropriate given the rarity of the disease, expertise of the NIH research team and potential benefits that are not available elsewhere. We will ensure that appropriate safeguards are in place per SOP 14F if the situation arises.

11.7 Justification for sensitive procedures

Not applicable

11.8 Training of investigators

The Principal Investigator has verified that all individuals working on this protocol required to take HRPP training under OHSRP Policy 201 have completed all required training.

12. Anticipated Benefit

The treatment has the potential to provide a direct benefit to the patient by reducing the effect of the underlying disease. The complete natural history of liver disease in NPC1 has not been defined. This is primarily due to early death secondary to neurological disease. As therapies are developed that slow neurological disease progression, it is likely that other aspects of the disease will become apparent. Chronic liver disease in NPC1, like chronic liver disease due to other etiologies, can lead to development of hepatocellular carcinoma.

This study will improve understanding of the safety and potential efficacy effects of administering IV VTS-270 in patients with NPC1. It also will provide us with information related to liver disease and biomarkers that will be of use in the development of other therapies. Participants and families may directly benefit from knowing that they are helping to increase our understanding of this devastating disease and participating in the development of potential therapies that may help others in the future.

Participants may directly benefit from having disease specialists directly involved in their medical care.

No financial compensation will be offered to patients, guardians, or families. Travel, lodging, and per diem expenses will be covered per NICHD and NIH policy.

13. Classification of Risk

13.1 Consenting adults

This study should be classified as more than minimal risk. The phone screening aspect of the protocol is not greater than minimal risk.

13.2 For adults unable to provide consent

Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual. The phone screening aspect of the protocol is not greater than minimal risk.

13.3 For children

45CFR46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child. The phone screening aspect of the protocol should be classified as 45CFR46.404 Research not involving greater than minimal risk.

13.4 Overall risk benefit consideration

NPC1 is a lethal disease with significant morbidity. Currently there are no approved therapies. The risks of this study are reasonable in relation to the potential benefit.

14. Consent Documents and Process

14.1 Consent process

Written informed consent will be obtained from patients or guardians as applicable to the specific situation prior to any intervention under this protocol. The informed consent form (ICF), as specified by the NIH IRB, must follow the Protection of Human Subjects regulations listed in the CFR, Title 21, Part 50.

Verbal or written screening for inclusion/exclusion criteria can be conducted prior to obtaining informed consent. Investigators may assist families in meeting eligibility requirements related to miglustat and dietary supplements prior to enrollment. Investigators may assist in obtaining laboratory testing to determine if a potential participant is likely to meet inclusion criteria related to serum transaminase levels.

Screening tests (such as NPC1 mutation analysis or blood chemistry testing) or evaluations may be conducted under other NICHD IRB approved protocols. Data collected under protocol 06-CH-0186 may be used for determining eligibility requirements.

The background of the proposed study and the benefits and risks of the procedures and study will be explained to the subjects. Either the Principal Investigator or a designated Associate Investigator will obtain consent. The original signed and dated informed consent will be placed into subject's NIH Clinical Center medical record. A copy will be given to the patient/guardian.

See sections 11.4 and 11.5 regarding consent/assent process in children and cognitively impaired adults.

14.2 Non-English–Speaking Participants

If a non-English speaking participant is eligible for enrollment, the participant will be provided with the CC Short Written Consent Form for Non-English-Speaking Research Participants in the participant's native language and a verbal explanation of the purpose, procedures and risks of the study as described in MAS Policy M77-2, NIH HRPP SOP 12 and 45 CFR 46.117(b)(2). The IRB-approved English consent form will serve as basis for the verbal explanation of the study. The investigator will obtain an interpreter unless the investigator is fluent in the prospective participant's language. The interpreter will be someone who is independent of the participant (i.e., not a family member). Interpretation servicesprovided by the CC will be used. The interpreters will interpret the IRB-approved English consent form and facilitate discussion between the participant and investigator.

The IRB-approved English consent form will be signed by the investigator obtaining consent and a witness to the oral presentation. The CC Short Written Consent Form will be signed by the participant and a witness who observed the presentation of information. The interpreter may sign the consent document as the witness and, in this case, will note "Interpreter" under the signature line. A copy of both signed forms will be provided to the participant to take home. The investigator obtaining consent will document the consent process in the participant's medical record, including the name of the interpreter.

We request prospective IRB approval of the use of the short form for up to a maximum of 5 separate encounters in a given language and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form. Should we reach the threshold of 5, we will notify the IRB of the need for an additional use of the Short Form and that we will have that consent document translated into the given inherent language.

14.3. Consent documents

Adult patient/Guardian for impaired adult or child

Minor assent

Intrathecal Consent

Screening Consent

15. Data and Safety Monitoring

15.1 Safety Monitoring

This is an unblinded trial, thus it can be monitored by the Principal Investigators in conjunction with Associate Investigators. The Principal Investigator is responsible for all aspects of the study. Regular, typically weekly, meetings will be held by the research staff to review status of all subjects, potential issues and possible adverse events.

This protocol does not meet the criteria as outlined in the NIH HRPP SOP 17 for data to be submitted to a data safety monitoring committee.

15.2 Data Monitoring

The research team will be responsible for monitoring data. The Principal Investigator is responsible for data integrity. Although all members of the research team will participate in data collections and review, Kisha Jenkins RN is the designated lead who will review data for accuracy and completeness.

15.3 IRB and FDA documentation

Protocol documentation related to IRB and FDA will be maintained in IRIS until NIH transfers all protocols to a centralized system

16. Quality Assurance

Quality assurance and quality control systems with written SOPs will be implemented and maintained to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

NICHD Office of the Clinical Director will perform quality assurance audits of this protocol consistent with applicable policy.

NICHD Office of the Clinical Director will contract for outside quality assurance audit of this protocol consistent with applicable policy.

17. Reporting of Unanticipated Problems, Adverse Events and Protocol Deviations

17.1 Definitions

Adverse event: An adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction: This is defined as any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, ‘‘reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Life-Threatening AE or Life-Threatening Suspected Adverse Reaction: An AE or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of the Investigator/Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious Adverse Event or Serious Suspected Adverse Reaction: An AE or suspected adverse reaction is considered ‘‘serious’’ if, in the view of the Investigator/Sponsor, it results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of hospitalization
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect

Unexpected AE or Unexpected Suspected Adverse Reaction: An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the protocol or consent, or is not listed at the specificity or severity that has been observed.

17.2 Adverse Event Classification

Relationship to Investigational Drug: The following two classifications should be used when evaluating the relationship of AEs and serious adverse events (SAEs) to the investigational drug:

1. Unrelated: no temporal association or definitely due to an alternative etiology

2. Unlikely Related: no clear temporal association or good evidence for a more likely alternative etiology

3. Possibly Related: temporal association, evidence exists for alternative etiology

4. Likely Related: temporal association follows a suspected response pattern (based on similar agents), a more likely alternative etiology unlikely

5. Definitely Related: clear temporal association follows a known response pattern, clear evidence to suggest a causal relationship, there is no alternative etiology.

17.3 Severity of an Adverse Event

Severity will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Published: 27 November 2017).

17.4 Investigator Reporting

Reportable events will be tracked and submitted to the IRB as outlined in policy 801.

Relatedness to the research of all serious adverse events will be determined by the PI in consultation with the SD.

Deaths will be reported to the Scientific Director within 7 days after the PI first learns of the event.

17.5 Documentation of Adverse Events

Patients will be evaluated and interviewed to identify AEs during the course of the study. AEs may also be identified through clinical and neurological examinations, laboratory tests, etc. Any events occurring prior to dosing will be recorded on the Medical History CRF. Events occurring after administration of the first dose of study medication will be recorded on the AE CRF. AE that occur up to and including 30 days after administration of the last dose of study drug must be reported.

All AEs spontaneously reported by the patient or in response to a question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the Adverse Event Form for that visit. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the AE CRF, unless otherwise stated in the protocol. AE information recorded on AE CRFs will be entered into the database on an ongoing basis.

For SAEs, a Serious Adverse Event Form must also be completed with as much information as possible and submitted in the time frame described below. When new significant information is obtained as well as when the outcome of an event is known, the Investigator should record the information on a new SAE form. If the patient was hospitalized, a copy of the discharge summary and any other

relevant hospital records (e.g. admission report, laboratory test results, etc., must be included as part of the patient medical file).

All AEs considered to be related to study medication and all SAEs will be followed until resolved or until stable.

17.6 Non-Reportable Events

The following data will be collected but the following will not be reported to the NICHD IRB as adverse events.

1. Findings present at initial evaluation.
2. Abnormal laboratory tests that have no clinical consequence.
3. Abnormal clinical tests in which the clinical response would be considered standard care (such as iron supplementation of iron deficiency anemia) and are unlikely to be related to the protocol.
4. Problems listed in Table 2 unless increase in frequency is noted.

17.7 Protocol Deviations

The following anticipated minor deviations in the conduct of the protocol will not be reported to the NCIHD IRB unless they occur at a rate greater than that which is anticipated to occur (frequency will be assessed over ten protocol admissions).

	Expected Frequency
Inability to obtain a blood or urine sample	20%
Technical issues preventing analysis of a blood sample (e.g. hemolysis)	20%
Procedure or sample not obtained at specified time	20%
Admission occurring outside of the defined time range	20%

Not obtaining a sample/data related to an exploratory endpoint will not be considered a deviation.

18. Alternatives to Participation

There are no approved therapies for NPC1. Potential participants have the option of requesting HPβCD under an expanded access IND or participating in clinical trials that are not associated with the NIH.

All NPC1 patients remain eligible for enrollment or continued participation in our Natural History protocol (06-CH-0186).

19. Privacy

Research activities will be conducted in a manner to protect privacy to the extent possible.

Table 2. Adverse events associated with NPC1

Category	Adverse Event
HEENT	Eyes Ptosis Abnormal eye movements (including vertical supranuclear gaze palsy and abnormalities of both vertical and horizontal eye movements)
	Audiologic Progressive high frequency hearing loss Abnormalities in Behavioral Hearing tests and Auditory Brain Stem Responses
	Oromotor/Speech Dysarthria Dysphagia, choking/gagging on food or saliva Copious secretions/drooling
Respiratory	Aspiration
	Aspiration pneumonia
	Sleep apnea
Gastrointestinal/ Genitourinary	Hepatomegaly
	Elevated liver enzymes
	Splenomegaly
	Gastrostomy tube related to dysphasia
	Bladder/bowel incontinence
	Diarrhea
	Constipation
Lymphatic	Enlarged tonsils and adenoids
Hematologic	Epistaxis
	Thrombocytopenia and prolonged PT/PTT
	Decreased serum iron, % saturation (not typically associated with low MCV)
Musculoskeletal/Extremities	Hyperreflexia, clonus
	Motor impairment Gross motor ataxia; impaired ambulation, balance, Coordination; decreased muscular strength; muscle contractures Fine motor ataxia, tremor
Neurological	Seizures
	Cognitive Impairment:
	Learning difficulty, long/short term memory loss
	Sleep Disruptions:
	Gelastic cataplexy
	Narcolepsy
	Sleep schedule inversion
	Fatigue, daytime sleepiness
Psychiatric/Behavioral	Mood swings, diagnosis of major depressive disorder, bipolar disorder, schizophrenia
	ADD/ADHD diagnosis (not more common than in general pediatric population)

ADD: attention deficit disorder; ADHD: attention deficit hyperactivity disorder; HEENT: head, eyes, ears, nose, throat; MCV: mean corpuscular volume

20. Confidentiality

20.1 Research Data and Medical Records

To maintain patient privacy, all CRFs, study drug accountability records, study reports, and communications will identify the patient by the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Research data will be maintained on password protected computers. Laptops containing clinical information will be encrypted per NIH policy. Hard copy patient records will be maintained in secured files/offices.

Participants/guardians will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual patients will not be used.

20.2 Stored samples

The NICHD Biorepository will be used to store samples. Samples will be coded. Working aliquots and samples sent to collaborators will be coded. Samples sent to a clinical, CLIA certified laboratory will be labeled with patient identifiers and the report will become part of the participants NIH medical record.

21. Conflict of Interest

NIH guidelines on conflict of interest will be distributed to all investigators.

Dr. Forbes D. Porter has been awarded or has filed patent application related to the identification and use of biomarkers in Niemann-Pick disease type C. Some of these biomarkers will be tested in this protocol. Additional patent applications may be filed by institutions involved in this study that relate to the treatment or monitoring of therapy for NPC1.

Dr. Forbes D. Porter and NICHD have a Cooperative Research Agreement with Vtesse, Inc for the development of intrathecal VTS-270. Vtesse, Inc. has been acquired by Sucampo which has now been acquired by Mallinckrodt. Dr. Porter is a Co-Principal Investigator for the Vtesse, Inc. Sponsored Phase 2b/3 study of

intrathecal VTS-270. Dr. Porter does not receive any compensation from Vtesse, Sucampo or Mallinckrodt.

Mallinckrodt will provide the VTS-270 for this study and may provide additional support to facilitate completion of this study. Mallinckrodt may use data obtained from this study to develop VTS-270 as a commercial product. Personal identifiers will not be supplied to Mallinckrodt. This CRADA has been reviewed by NIH ethics. Other formal agreements, such as a confidentiality, material transfer or clinical trial agreements, may be established between NICHD and Mallinckrodt to facilitate this trial. All agreements will be reviewed by NIH ethics per policy.

Collaborating or associate investigators who are not part of the NIH may have funding or consulting relationships with pharmaceutical companies developing therapies for NPC1. Although these collaborating or associate investigators provide invaluable input, they are not responsible for the implementation of this protocol at the NIH Clinical Center. Although members of the team may interact with pharmaceutical companies as part of their official duties, NIH investigators do not receive financial compensation or have personal financial holdings (above the limits set by the NIH) with pharmaceutical companies.

This protocol is supported by an Opportunities for Collaborative Research at the NIH Clinical Center U01 grant (U01 HD090845). The extramural principal investigator is Dr. Daniel S. Ory, Washington University. The intramural principal investigator is Dr. Forbes D. Porter, NICHD.

22. Technology Transfer

We will establish a material transfer agreements and notify the NICHD IRB consistent with current applicable NIH DIR policy.

Material transfer agreements with commercial entities will be submitted as amendments to this protocol prior to implementation.

23. Research and Travel Compensation

No financial compensation will be offered to patients, guardians, or families. Travel, lodging, and per diem expenses will be covered per NICHD and NIH policy.

NIH employees or staff who participate during work hours must have permission from their supervisor.

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Attachment 1: Schedule of Events

Consent	X																		
Medical History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical/research labs (bloodwork)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm subject eligibility	X																		
Dosing group assignment	X																		
Fibroscan	X												X						X
Audiology	X			X															
Abdominal ultrasound	X											X							X
Chest x-ray	X																		
NPC clinical severity scale	X													X					X
Pulmonary function test	X																		
Intrathecal VTS-270 administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IV study drug administration				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Baseline and timing in this section is relative to the initiation of peripheral VTS-270 therapy with baseline defined as -0.5 to 0 months. For 6 and 12-month assessment 6 ± 1 and 12 ± 1 months is acceptable.																			
For testing performed monthly, ± 1 week is acceptable.																			
The baseline admission testing may be performed in conjunction with an admission for IT VTS-270 administration. The baseline and first drug administration visit may be combined.																			